STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

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I hereby declare that the thesis entitled "**STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"** submitted towards partial fulfillment of the requirements for the award of **MD in General Medicine** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Harmeet Pal Singh Dhooria**, Associate Professor, Department of Medicine, **Dr. Dinesh Gupta**, Professor & Head, Department of Medicine & **Dr. Parminder Singh,** Professor & Head, Department of Endocrinology. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my Family

&

Teachers

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Dr. Ujjwal Mahajan…

LIST OF ABBREVIATIONS

ABI	Ankle brachial index
ADA	American diabetes association
CAN	Cardiovascular autonomic neuropathy
CART	Cardiovascular autonomic reflex testing
CKD	Chronic kidney disease
CRF	Chronic renal failure
CVR	Cardiovascular reflex
DM	Diabetes Mellitus
DSPN	Distal symmetrical polyneuropathy
ED	Erectile dysfunction
HRV	Heart rate variation
MI	Myocardial infarction
NPDR	Non proliferative diabetic retinopathy
PAD	Peripheral artery disease
PDR	Proliferative diabetic retinopathy
CAN+	Cardiovascular autonomic neuropathy positive
CAN-	Cardiovascular autonomic neuropathy negative

ABSTRACT

Introduction: Cardiac autonomic neuropathy (CAN) is a potentially serious and underdiagnosed complication of diabetes mellitus (DM) strongly associated with increased risk of cardiovascular mortality.

Objectives: To estimate the pattern and frequency of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus patients.

Methods: The study was conducted in the Department of Medicine, Department of Endocrinology and its Allied Specialities, Dayanand Medical College and Hospital, Ludhiana. 100 Type 2 Diabetes Mellitus OPD and indoor patients were enrolled for this study conducted over a period of one and a half years.

Results: Mean age of study group was 56.57±11.86 years with male: female ratio of 1.43: 1. The mean duration of diabetes of study population was 8.83±5.55 years. The prevalence of CAN was found in 67 out of the 100 patients (67%) studied. Maximum i.e 22% had early CAN, 9% had definite CAN, 18% had severe CAN and 18% had atypical CAN. Parasympathetic testing was positive in 59 (59%), sympathetic testing was positive in 37 patients (37%) and combined parasympathetic and sympathetic testing were positive in 29 patients (29%). CAN positivity was associated with increasing age, greater duration of diabetes, diabetic neuropathy and albuminuria. HbA1c, gender and dyslipidemia had no effect on presence of CAN. Erectile dysfunction and diabetic retinopathy were more common in CAN+.

Conclusion: 67% of our study subjects had cardiac autonomic neuropathy which is very significant**.** So, CAN testing using simple bed side tests in patients of diabetes can help in early identification of CAN**.** Such CAN patients should be advised about tight glycemic control, lifestyle modifications and symptomatic treatment of orthostatic hypotension to prevent the further complications of CAN.

Keywords: Diabetes mellitus type 2, Cardiac autonomic neuropathy

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INTRODUCTION

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia precipitating because of the complete (Type 1 DM) or partial (Type 2 DM) absence of the insulin hormone. The recent estimates suggest that worldwide almost 350 million people suffer from diabetes, and these estimates are expected to get doubled by the year 2030 if no active measures are taken. The epidemiological studies across the world have revealed a significant increase in the incidence of diabetes. [1] Type 2 diabetes mellitus is the most common type of diabetes in the world constituting 90% of the diabetic population. Diabetes mellitus is a leading public health care problem in developing and developed world, with increasing incidence and long term complications. The triad of neuropathy, retinopathy and nephropathy are the characteristic complications of chronic diabetes mellitus. [2]

Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus (DM) that is strongly associated with approximately five-fold increased risk of cardiovascular mortality. Cardiac Autonomic Neuropathy (CAN) causes damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. CAN manifests in a spectrum of things, ranging from resting tachycardia and fixed heart rate (HR) to development of “silent” myocardial infarction. The main predictors for the development of CAN in patients with T2DM are age, gender, ethnicity and presence of microvascular complications (nephropathy, retinopathy, and peripheral neuropathy). In a cohort of 1000 Type 2 diabetes mellitus patients, the development of CAN at 7.5 years of follow-up was correlated with older age and the presence of microvascular disease. So Screening for CAN should be performed in T2 DM patients at diagnosis and T1 DM patients after 5 years of disease, in particular those at greater risk for CAN due to a history of poor glycemic control (HbA1c > 7%). [3]

India is the diabetes capital of the world with 41 million Indians suffering from diabetes. Cardiac autonomic neuropathy (CAN) is often an underdiagnosed complication of diabetes mellitus (DM) and is associated with increased mortality and morbidity. The prevalence of CAN is approximately 31–73% in type 2 DM and the annual incidence has been reported to be 2%. CAN is initially subclinical and becomes symptomatic only in the later stages of the disease. Thus identifying patients with CAN is important for early initiation of intensive interventions. [4]

Diabetes-related CAN results from complex interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death. Hyperglycemia is thought to be a primary culprit, spurring a cascade of multiple complex mechanisms and pathways that induce oxidative stress and toxic glycosylation products—ultimately resulting in neuronal dysfunction and death. The pathogenesis of CAN is complex and involves a cascade of pathways activated by hyperglycaemia resulting in neuronal ischaemia and cellular death. In addition, autoimmune and genetic factors are involved in the development of CAN. Autonomic nervous system dysfunction occurs as a classic complication of diabetes once other causes have been excluded which includes (differential diagnosis):

- Addison’s disease
- Hypopituitarism
- Pheochromocytoma
- Hypovolemia
- Use of Medications, with anticholinergic or sympatholytic effects (vasodilators, sympathetic blockers) should be excluded [5,6]

CAN is associated with following manifestations: [6]

- reduction in heart rate variability
- resting tachycardia
- orthostatic hypotension
- sudden death syndrome
- exercise intolerance
- gastrointestinal manifestations that includes diabetic gastropathy, enteropathy and colonic hypomotility
- urogenital manifestations that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction
- sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis
- abnormal pupillary function
- hypoglycemic unawareness
- hypoglycaemia induced autonomic failure

The risk of developing autonomic dysfunction in DM depends on several factors. However, two of them are common to both type 1 DM and type 2 DM: Degree of glycemic control and disease duration. Inadequate glucose control plays an important role in the initial pathophysiology microcirculation dysfunction due to nitric oxide (NO) loss, oxidative stress (OS) and accumulation of free radicals with lesion of schwann cell as well as in its progression (neuronal apoptosis and axonal degeneration). [6]

Diabetic autonomic neuropathy is a widespread disorder potentially involving adrenergic, cholinergic, dopaminergic autonomic fibers as well as peptidergic neurons. The duration of diabetes is an independent factor for developing CAN irrespective to diabetes type. Poor glycemic control is a major risk factor for CAN progression. [7,8] Diabetes affects the autonomic (as well as the peripheral) nervous system in an ascending length-dependent manner. The vagus nerve, which anatomically is the longest autonomic nerve and physiologically

mediates 75% of the overall parasympathetic activity, tends to be involved early in the course of CAN development. The early stages of CAN therefore involve reduction in parasympathetic activity, which results in sympathetic predominance. This increase in sympathetic tone continues until the latest stage of CAN when sympathetic denervation ensues, which spreads gradually from the apex to the base of the heart. [7]

Diabetic patients also run a 2-3 folds higher risk of cardiovascular morbidity and mortality during surgery. There is an association between CAN and intraoperative hypothermia and orthostatic hypotension, although the fall in blood pressure may also be asymptomatic. One potential cause of higher mortality during surgery in such patients could be severe but asymptomatic ischemia, which can induce lethal arrhythmias. [9] The increase in QT interval in diabetic patients with autonomic neuropathy might explain their high risk for sudden death. Long QT syndrome in diabetic patients with CAN was found as an independent risk factor for sudden death. [10]

Despite similarities in the pathogenesis of CAN and DPN, they are not the same disease. Early determination of CAN is vital to the success of therapeutic input, as it has been suggested that cardiovascular denervation may be reversible if diagnosed soon after onset.

The aim of CAN treatment is symptom control or slowing progression. CAN treatment is a complex process that includes: Lifestyle modification; reducing insulin resistance, intensive glycemic control, antioxidants, α-lipoic acid (ALA), aldose reductase inhibitors, acetyl-carnitine, vitamins i.e all fat-soluble and vitamin B1; correction of vascular endothelial dysfunction; prevention and treatment of thrombosis; in severe cases-treatment of orthostatic hypotension. Current methods use a combination of non-pharmacological and pharmacological approaches, non-pharmacological includes lifestyle modification, intensive glycemic control, and adequate control of underlying risk factors, such as hyperlipidemia and hypertension whereas pharmacological includes use

of ACE inhibitors, beta blockers, role of vitamin E, alpha-lipoic acid and treatment of orthostatic hypertension. [11]

AIMS & OBJECTIVES

To estimate the pattern and frequency of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus patients.

REVIEW OF LITERATURE

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia precipitating because of the complete (Type 1 DM) or partial (Type 2 DM) absence of the insulin hormone [1] .The Criteria for diagnosis of Diabetes Mellitus was approved by American Diabetes Association.

ADA CRITERIA FOR THE DIAGNOSIS OF DIABETES [12]

1. HbA1c >=6.5 %
   OR
2. Fasting plasma glucose ≥ 126 mg/dl. (Fasting is taken as no energy intake for 8 hours at least)
   OR
3. 2 hour plasma glucose ≥ 200 mg/dl in an OGTT (to be done using a 75 g glucose load)
   OR
4. In a patient with classic symptoms of hyperglycemia, a random plasma ≥ 200 mg/dl

COMPLICATIONS OF DIABETES MELLITUS

Epidemiology and Pathogenesis of Diabetic Complications: There is growing evidence that the underlying mechanisms in the pathogenesis of diabetic complications include certain genetic and epigenetic modifications, nutritional factors and sedentary lifestyle. Findings from The Irish Longitudinal Study on Ageing," has recognized ageing, male gender, smoking, low level of physical activity, and high cholesterol as independent predictors of macrovascular complications. Conversely, smoking, hypertension, and duration of DM over 10 years proved to be predictive factors for microvascular complications. [13] Arif ZA et al concluded that cardiac autonomic neuropathy is common in diabetic patients in Pakistan. The clinician should identify early CAN by doing simple tests. The study also demands for large scale population based studies in future. [9] Pop busui et al concluded that CAN is a serious

chronic complication of diabetes and an independent predictor of cardiovascular disease mortality. CAN is associated with a poor prognosis and poor quality of life. [14] Brijadar et al concluded that in the present study, the overall prevalence of autonomic neuropathy in diabetes mellitus was 58% at the tertiary care hospital. [15] Aggarwal S et al concluded that the prevalence of DAN in the cohort studied was 70%. Amongst these, 22.9% had severe autonomic dysfunction with prevalence of definite and early neuropathy being 40% and 37% respectively. [16]

Complications of Diabetes mellitus can be divided into micro vascular and macro vascular complications: [17]

Micro vascular complications:

1) Neuropathy
2) Nephropathy
3) Retinopathy

Macro vascular complications:

1) Cardiovascular disease
2) Cerebrovascular disease
3) Peripheral vascular disease

MICROVASCULAR COMPLICATIONS

DIABETIC NEUROPATHY: Diabetic neuropathy comprises a number of different syndromes, each with a range of clinical and subclinical manifestations. The main groups of neurologic disturbance in diabetes mellitus include: [18]

(1) subclinical neuropathy determined by abnormalities in electrodiagnostic and quantitative sensory testing
(2) diffuse clinical neuropathy with distal symmetric sensorimotor and autonomic syndromes
(3) focal syndromes

The diagnostic definition of diabetic peripheral neuropathy is given by The Toronto Diabetic Neuropathy Expert group as [19]

1. Possible DSPN: The presence of symptoms or signs of DSPN may include the following:
Symptoms: decreased sensation, positive neuropathic sensory symptoms (e.g., “asleep numbness”, prickling or stabbing, burning or aching pain) predominantly in the toes, feet, or legs; or Signs: symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.

2. Probable DSPN: The presence of a combination of symptoms and signs of neuropathy include any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes.

3. Confirmed DSPN: The presence of an abnormality of NCV and a symptom or signs of neuropathy confirm DSPN.

4. Subclinical DSPN: The presence of no signs or symptoms of neuropathy are confirmed with abnormal NCVs or a validated measure of small fibre neuropathy.

In a study done Aaron et al 25% of patients with Diabetes Mellitus type 2 were tested and 50% of them were found to have diabetic neuropathy after simple clinical tests such as ankle jerk and vibration sense. But almost 90% were positive for neuropathy after being tested with sophisticated autonomic function tests. [18]

Diagnosis is made by difference in symptoms between small and large fibre neuropathy. A careful history is important diagnosis of peripheral neuropathy. Patients with small fibre neuropathy presents with burning, electric shock or piercing sensation and with large fibre neuropathy presents with tingling sensation, difficulty in balancing and numbness.

DIABETIC RETINOPATHY

Diabetic retinopathy is the most frequent cause of new cases of blindness among people aged 20–75 years. Diabetic retinopathy progresses from mild nonproliferative abnormalities, characterized by increased vascular permeability, to moderate and severe nonproliferative diabetic retinopathy (NPDR), characterized by vascular closure, to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. The risk factors include duration of diabetes, glycemic control and status of blood pressure control. Certain studies postulate that puberty and pregnancy accelerates Diabetic retinopathy.

Diagnosed is done by Dilated indirect ophthalmoscopy and Fundus photography. Fundus examination after 3-5 years of diagnosing diabetes Mellitus type 1 is recommended on yearly basis and at the time of diagnosis of diabetes mellitus type 2 is recommended on yearly basis. [20]

DIABETIC NEPHROPATHY

Diabetic nephropathy is one of the leading cause of end stage kidney disease. [21] The diabetic patients with more than 500mg / 24 hours is defined as diabetic nephropathy. The number of diabetic nephropathy has become twice among renal transplant patients from the year 1990-2000.This increase in rate was slowed down due to early diagnosis and prevention of nephropathy. Diabetic nephropathy is also associated with increased cardiovascular mortality. Diabetic nephropathy is the largest cause for chronic kidney disease among the renal transplant patients. Simplest tool to diagnosis is Urine spot albumin test. [22]

TABLE 1: STAGES OF DIABETIC NEPHROPATHY [21]

STAGE	DESIGNATION	GFR	ALBUMIN EXCRETION
I	Hyperfunction/ Hyperfiltration	High(≥150 ml/hr)	≤ 30 mg/day
II	Normoalbuminuria	High if blood sugar not controlled	<30 mg/day (Increased in stress situations)
III	Incipient nephropathy, Microalbuminuria	High if blood sugar not controlled	30-300 mg/day
IV	Overt nephropathy	Normal to advanced reduction, GFR declines in this stage	>300 mg/day
V	End stage kidney disease	< 15/min	>300 mg/day

MACROVASCULAR COMPLICATIONS

CARDIO AND CEREBROVASCULAR DISEASE: Diabetes causes a major prevalence of Myocardial Infarction or Stroke as its complications. Stroke prevails in the older age group, demonstrating a closer age-dependence for cerebrovascular complications and with the duration of diabetes. Studies demonstrate and confirm that diabetes especially that of long duration is an important pathogenetic factor for the cardio-cerebrovascular complications. Other risk factors include obesity, hyperuricemia and albuminuria. Diagnosis is made by detailed history and physical examination and by bedside ECG. [23]

PERIPHERAL VASCULAR DISEASE

Peripheral artery disease (PAD) is defined as the atherosclerotic occlusive disease of lower extremities. Most common symptom in PAD is claudication pain. DM is also associated with more severe below-the-knee PAD unlike smoking which involves proximal vessels. An ABI (ankle brachial index) of ≤0.90 is commonly used in both clinical practice and epidemiological research to diagnose PAD. [24]

CLASSIFICATION OF DIABETIC AUTONOMIC NEUROPATHIES

CAN, that is associated with reduction in HRV, resting tachycardia, orthostatic hypotension and sudden death syndrome; gastrointestinal manifestations that includes diabetic gastropathy, enteropathy and colonic hypomotility; urogenital manifestations that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction; sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis; abnormal pupillary function; hypoglycemic unawareness.

CLASSIFICATION

1. Subclinical phase: Decreased HRs variability

2. Early phase: Resting tachycardia

3. Advanced stage: Exercise intolerance; Cardiomyopathy with left ventricular dysfunction; Silent myocardial infarction [3,6]

PATHOGENESIS OF CAN

According to Pop-Busui et al, diabetes-related CAN results from complex interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death. Hyperglycemia is thought to be a primary culprit, spurring a cascade of multiple complex mechanisms and pathways that induce oxidative stress and toxic glycosylation products—ultimately resulting in neuronal dysfunction and death (Figure below). Hyperglycemia increases mitochondrial production of free reactive oxygen species, thereby causing oxidative damage to the microvasculature supplying these peripheral nerves. [14]

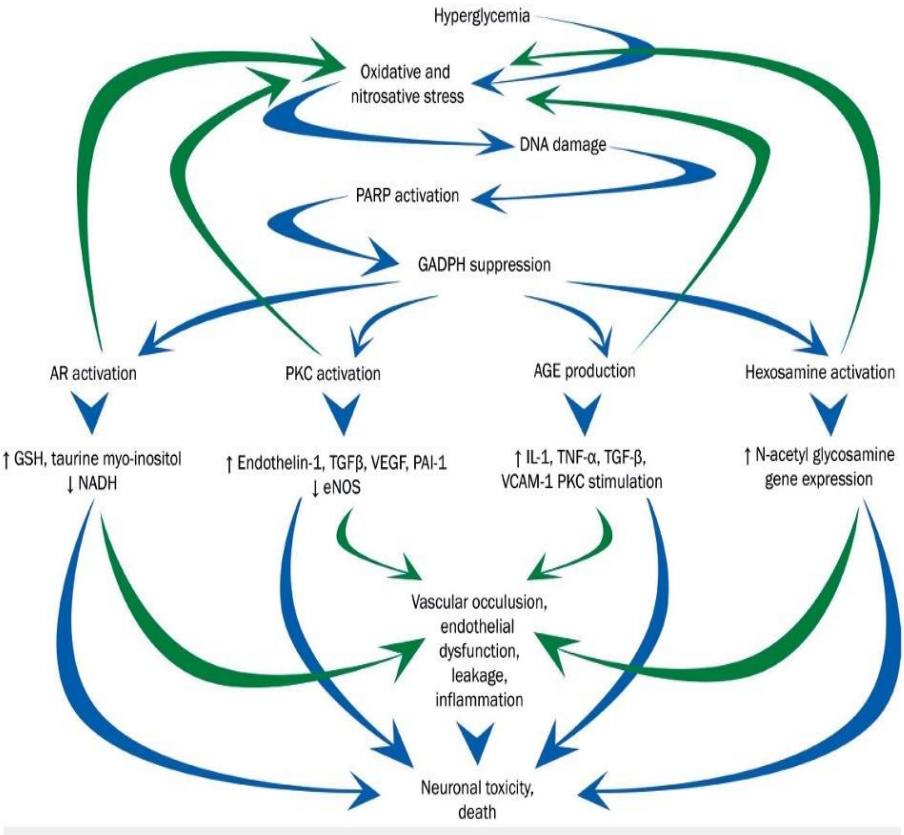

FIGURE 1: Pathogenesis of (Cardiovascular Autonomic Neuropathy) CAN [5]

CARDIAC AUTONOMIC DYSFUNCTION

Diabetes-associated cardiovascular autonomic neuropathy (CAN) damages autonomic nerve fibers which innervates the heart and blood vessels. It is a severely debilitating complication that often decreases survival in patients with diabetes in turn causing abnormalities in heart rate and vascular dynamics. [5]

EPIDEMIOLOGY OF CAN

The reported prevalence of DAN varies, depending on whether studies have been carried out in the community, clinic, or tertiary referral center. The variance among prevalence studies also reflects the type and number of tests performed and the presence or absence of signs and symptoms of autonomic neuropathy.

Ziegler et al. evaluated the prevalence of CAN in 1,171 diabetic patients (647 type 1 diabetic patients, 524 type 2 diabetic patients) randomly recruited from 22 diabetes centers in Germany, Austria, and Switzerland. The study found that 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had abnormal findings in more than two of six autonomic function tests. If more strict criteria were used (i.e., abnormalities present in least three of six autonomic function tests), the prevalence of CAN was 16.8% for individuals with type 1 diabetes and 22.1% for individuals with type 2 diabetes. Another study group observed nearly an identical prevalence rate (16.6%) for individuals with insulin-dependent diabetes.[25] Memon A et al concluded that CAN was observed in 29 (41.4%) using Bellavere's score system. The CAN score may be used as feasible and reproducible bedside clinical test in diabetic patients.[26] Sukla P et al concluded that overall prevalence of cardiac autonomic neuropathy among diabetic patients was found to be as 53.2%. Even though cardiac autonomic neuropathy can be detected by various invasive tests, noninvasive tests remain a key tool to detect it in the remote settings in a cost-effective and user-friendly manner without making people visit higher centers.[1] Bhuyan K et al concluded that CAN

is a common microvascular complication in type 2 DM with prevalence of 70%. The duration of diabetes, age, and severity of nephropathy are its significant determinants and hence optimal glycemic management at early stages of diabetes may prevent development of CAN.[4]

CLINICAL MANIFESTATIONS OF CAN

Exercise intolerance: Autonomic dysfunction can impair exercise tolerance. [27] In a study of individuals with and without CAN, Kahn et al. [28] showed a reduced response in heart rate and blood pressure during exercise in individuals with CAN. Roy et al. [29] demonstrated a decreased cardiac output in response to exercise in individuals with CAN. Dimitropoulos G et al concluded that CAN is very common and is an underdiagnosed complication of DM. CAN is associated with significant increase in morbidity and mortality and plays an important role in the development of diabetic cardiomyopathy and silent ischaemia. Clinicians interpreting exercise tolerance testing should be aware of the reduced accuracy of this test in patients with CAN. [7]

Intraoperative cardiovascular lability: Hemodynamic changes occur during surgery for individuals with and without diabetes. Burgos et al. [30] found that vasopressor support was needed more often in diabetic individuals with autonomic dysfunction than in those without. The normal autonomic response of vasoconstriction and tachycardia did not completely compensate for the vasodilating effects of anesthesia. Studies also show relationship between CAN and more severe intraoperative hypothermia.

Orthostatic hypotension: Orthostatic hypotension is defined as a fall in blood pressure (i.e., >20 mmHg for systolic or >10 mmHg for diastolic blood pressure) in response to postural change, from supine to standing. Chen HS et al concluded that Type 2 diabetic patients with abnormal CVR tests may have increased mortality, and those combined with postural hypotension have higher mortality than those without. Abnormal

CVR tests may be important predictors of mortality in Type 2 diabetes mellitus. [31] Aaron et al concluded that Diabetic CAN, a serious complication found in one fourth of type 1 and one third of type 2 diabetic patients, is associated with increased mortality and silent myocardial ischemia and may even predict the development of stroke. CAN is associated with a poor prognosis and may result in severe orthostasis, postural hypotension, exercise intolerance, enhanced intraoperative instability, and an increased incidence of silent MI and ischemia. It may be attributable to a functional abnormality or to organic structural damage to the different components of the autonomic nervous system. In patients with diabetes, orthostatic hypotension is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature. [27]

SILENT MYOCARDIAL ISCHEMIA: The cause of silent myocardial ischemia in diabetic patients is controversial and is mainly due to reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and thereby delay appropriate therapy. Of the 12 studies, 5 showed a statistically significant increased frequency of silent myocardial ischemia in individuals with CAN compared with individuals without CAN. Ambepityia et al. [32] measured the anginal perceptual threshold (i.e., the time from onset of 0.1 mV ST depression to the onset of angina pectoris during exercise) in individuals with and without diabetes. The perception of angina was severely impaired in the diabetic patients, allowing these individuals to exercise longer after the onset of myocardial ischemia. The delay in perception of angina was associated with the presence of cardiovascular autonomic dysfunction

SUDDEN CARDIAC DEATH: CAN is associated with an increased mortality risk in diabetics. This was described in longitudinal studies in the early 1990s showing a 50% increase in 5 year-mortality risk in patients with DM and autonomic neuropathy compared to those without

[7]. Similarly Bellavere et al concluded that sudden death is more common in patients with diabetic autonomic neuropathy. [10] A study by O'Brien [33] concludes that cumulative 5-year mortality rate was increased more than five-fold in those with autonomic neuropathy: 27 per cent vs. 5 per cent in those with normal autonomic function. One potential cause of sudden death may be due to asymptomatic ischemia, eventually inducing lethal arrhythmias. An autonomic imbalance resulting in QT prolongation may also predispose individuals to life-threatening cardiac arrhythmias and sudden death.

Aaron et al concluded CAN was significantly associated with subsequent mortality in both groups, although the magnitude of the association was stronger for those studies for which two or more measures were used to define CAN. The pooled relative risk for studies that defined CAN with the presence of two or more abnormalities was 3.45 (95% CI 2.66-4.47; $P < 0.001$) compared with 1.20 (1.02-1.41; $P = 0.03$) for studies that used one measure. [6] Mathur CP et al concluded that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other ANF tests. Further, QTc prolongation has linear positive correlation with the degree of CAN. It is inferred from the present observations that QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance. [34]

CLINICAL TESTING OF AUTONOMIC FUNCTION: In the early 1970s, Ewing et al. [35] proposed five simple noninvasive cardiovascular reflex tests (i.e. Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip) that have been applied successfully by many.

Serhiyenko VA et al concluded CAN is common and often underdiagnosed complication of DM which is strongly associated with

increased rate of cardiovascular morbidity and mortality. As the development and progression of cardiovascular denervation can be slowed down and is partly reversible in the early disease stages, it is recommended to perform screening for that complication among DM patients. A variety of methods can be used for CAN assessment, but the “gold” standard clinical tests are CARTs. The basic CAN prevention and treatment tools are intensive glycemic control, lifestyle modification and management of CVD risk, but the unified algorithm and known disease modifying treatment is lacking. [3]

Agashe S et al concluded that Diabetes-related CAN cause significant morbidity and mortality and is common in both type 1 and type 2 DM. The pathophysiological mechanisms leading to CAN are multifactorial and need further study. CAN in DM can be subclinical or present with a wide range of symptoms, ranging from resting tachycardia to orthostatic hypotension. Although CAN in DM is difficult to diagnose in the hospital setting, multiple tests of autonomic function are available in the outpatient setting for screening and definitive diagnosis. [5]

Basu et al concluded that the prevalence of cardiac autonomic neuropathy is 54%. Cardiac autonomic neuropathy is detected by various cardiac autonomic function tests. Symptoms of autonomic neuropathy are not as sensitive as the autonomic function tests to detect cardiac neuropathy. Therefore, assessment of autonomic cardiovascular reflexes affords a satisfactory method for the evaluation of CAN. [36]

TESTS TO ASSESS PARASYMPHATHETIC DYSFUNCTION [6]

1. Heart rate response to deep breathing (i.e beat-to-beat heart rate variation, R-R variation): The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while a heart monitor records the difference between the maximum and minimum heart rates.

Benichou T et al reported strong evidence for an overall decrease in HRV in T2DM patients. Both sympathetic and parasympathetic activity was decreased, which can be explained by the deleterious effects of altered glucose metabolism on HRV. The benefits of an HRV evaluation in assessing and monitoring the severity of T2DM should be further studied, given its potential as a non– invasive, reliable and pain–free measurement. [37]

2. Heart rate response to standing: This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. ECG tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15).

3. Heart rate response to valsalva manoeuvre: In healthy subjects, the reflex response to the valsalva manoeuvre includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in blood pressure and bradycardia after release of strain. In the standard valsalva manoeuvre, the supine patient connected to an ECG monitor, forcibly exhales for 15 s against a fixed resistance (40 mmHg) with an open glottis.

The response to performance of the valsalva manoeuvre has four phases and in healthy individuals can be observed as follows:

Phase I: Transient rise in blood pressure and a fall in heart rate due to compression of the aorta and propulsion of blood into the peripheral circulation. Hemodynamic changes are mostly secondary to mechanical factors.

Phase II: Early fall in blood pressure with a subsequent recovery of blood pressure later in the phase. The blood pressure changes are accompanied by an increase in heart rate. There is a fall in cardiac output due to impaired venous return causing compensatory cardiac acceleration, increased muscle sympathetic activity, and peripheral resistance.

Phase III: Blood pressure falls and heart rate increases with cessation of expiration.

Phase IV: Blood pressure increases above the baseline value (overshoot) because of residual vasoconstriction and restored normal venous return and cardiac output.

The Valsalva ratio is determined from the ECG tracings by calculating the ratio of the longest R-R interval after the manoeuvre (reflecting the bradycardic response to blood pressure overshoot) to the shortest R-R interval during or shortly after the manoeuvre (reflecting tachycardia as a result of strain).

TESTS TO ASSESS SYMPHATHETIC DYSFUNCTION [6]

1. Systolic blood pressure response to standing: Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by <10 mmHg in 30s.

2. Diastolic blood pressure response to sustained handgrip: In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. The normal response is a rise of diastolic blood pressure >16 mmHg, whereas a response of <10 mmHg is considered abnormal.

Test	Technique	Normal response and values
Beat-to-beat HRV	With the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at 6 breaths per minute, paced by a metronome or similar device	A difference in HR of > 15 beats per minute is normal and < 10 beats per minute is abnormal. The lowest normal value for the expiration-to inspiration ratio of the R-R interval decreases with age: age 20-24 yr, 1.17; 25-29, 1.15; 30-34, 1.13; 35-39, 1.12; 40-44, 1.10; 45-49, 1.08; 50-54, 1.07; 55-59, 1.06; 60-64, 1.04; 65-69, 1.03; and 70-75, 1.02
Heart rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03, borderline 1.01-1.03
Heart rate response to the valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is > 1.2, borderline 1.11-1.2
Systolic blood pressure response to standing	Systolic BP is measured in the supine subject. The patient stands and the systolic BP is measured after 2 min	Normal response is a fall of < 10 mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of > 30 mmHg
Diastolic blood pressure response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic BP is a rise of > 16 mmHg in the other arm, borderline 11-15 mmHg

FIGURE 2: CAN Testing Techniques and Interpretation [3]

CRITERIA INTERPRETATION AS PER EWING'S [35]

Normal = All tests normal or 1 test borderline.

Early = One of the three heart rate tests abnormal or two borderline.

Definite = Two heart rate tests abnormal.

Severe = Two heart rate tests abnormal + one or both BP tests abnormal or both borderline

Atypical= Any other combination of abnormalities

Giacomo Z et al concluded that CAN could be detected very early in type 2 diabetes. This study may suggest the importance of performing standardized cardiovascular autonomic tests after diagnosis of type 2 diabetes. [8] Sumaswi et al concluded that cardiovascular autonomic neuropathy is common in type 2 diabetic patients and can be recognized by simple bedside autonomic function tests. Prolonged QTc interval is an indicator for the presence of cardiovascular autonomic neuropathy in type 2 diabetic patients. [2]

TREATMENT APPROACH TO CAN

The treatment of CAN is mainly directed to slow down and reverse progression of CAN. However drugs available to halt or reverse the CAN are limited. Karupasamy G et al concluded that the exact prevalence of autonomic neuropathy in diabetes is precisely not known, however tests of autonomic function have shown impairment in roughly 40 to 50% of diabetic patients. Subclinical autonomic nerve damage occurs more widely in diabetes and may go unnoticed. It is assuming greater importance because of the implications for morbidity and mortality. Symptomatic autonomic neuropathy carries a worse prognosis than any other complication of diabetes. Prevention of autonomic damage with newer drugs, particularly in its earlier stage will reduce the mortality and morbidity significantly. Newer drugs have to be tried for comforting many

diabetics with clinical autonomic neuropathy afflicted with this condition in that at least the quality of life of with diabetic neuropathy will improve. [38]

Based on risk factors and pathogenesis following treatments are considered:

TIGHT GLYCEMIC CONTROL: Early observations by researchers that near-normal glycemic control seems to be the most effective way to delay the onset of CAN in type 1 diabetes has been confirmed by evidence from the DCCT. [39] Intensive insulin therapy has been shown to be effective at preventing multiple complications in patients with type 1 diabetes and is postulated to be effective for patients with type 2 diabetes, although clinical studies are underway in the latter. Emphasizing tight control for individuals with autonomic dysfunction should also include increased vigilance in glycemic monitoring and re-education of the patient with regard to hypoglycaemia as it is recognized that autonomic neuropathy may cause or contribute to the development of hypoglycaemic unawareness.

IMPORTANCE OF ADHERENCE TO DIET AND EXERCISE INTERVENTIONS

Lifestyle changes have shown to have beneficial impact on prevention of progression of CAN in the Steno-2 trial [40] and Diabetes Prevention Program (DPP) [41]. In Steno-2 study, patients with Type 2 DM and micro albuminuria were randomised to multifactorial cardiovascular risk factors intervention that included therapies like behavioural therapy (diet, exercise and smoking cessation) and pharmacological interventions (to blood pressure, lipids and hyperglycaemia control) or conventional treatments in accordance to national guidelines. After an average of about 7.8 years follow-up, the risk of developing CAN was significantly decreased in the intervention arm (i.e. 49% in intensive group versus 65% in conventional group, HR = 0.37, 95% CI : 0.18-0.79, P value =

0.002). In the DPP, lifestyle modifications demonstrated higher results in improving autonomic dysfunction (which was assessed with HRV and QT indexes) as compared to using metformin or placebo. Weight loss and daily aerobic exercise also decreases the chances of CAN.

THERAPIES IN CAN

There is limited data on the use of pharmacotherapy targeting specific pathways. Fisher LA et al concluded that CAN is very common and often undiagnosed in patients with DM. Intensive multifactorial intervention targeting lifestyle, glycemic control, and CVD risk factors prevents the development and slows the progression of CAN. Identifying patients with CAN is important, as CAN is associated with increased mortality, CVD, CKD, perioperative morbidity, and lower-limb complications. As such, these patients should receive appropriate follow up and preventive treatments to prevent or slow the progression of these complications. CAN should be diagnosed as per the Toronto Consensus Panel statement using standardized CARTs. Further research into the pathogenesis of CAN is important, in order to identify novel treatment targets and develop new therapies. [11] Using glucagon-like peptide1 analogues and also the dipeptidyl peptidase inhibitors have been cardioprotective [42] and neuroprotective properties [43], increasing the possibility of their use for treatment for peripheral neuropathy, also for autonomic neuropathy as well. There is also evidence to show that that vitamin E and C-peptide – both can improve HRV indices. In a RCT, vitamin E was compared to placebo and it managed to increase R-R interval ($P < 0.05$) and HF component of HRV (HF; $P < 0.05$) in about 50 patients with Type 2 DM for a period of 4 months. [44]

SYMPTOMATIC TREATMENT OF ORTHOSTATIC HYPOTENSION

Treatment of orthostatic hypotension is needed only in symptomatic patients. There are various strategies available, including change in lifestyle and behavioural measures and pharmacological measures. The former includes advice given to patients to avoid changes in body posture suddenly, to eat small and frequent meals, to avoid drugs that precipitate postural hypotension (like diuretics, TCAs, α-adrenoreceptor antagonists), to perform physical counter-manoeuvres (like leg crossing, stooping, squatting), to increase fluid as well as salt intake, to avoid physical activity that can lead to straining and to use garments over the legs and abdomen. Education of the patient and action to address reversible causes of orthostatic hypotension are the cornerstones of its treatment. Nevertheless, many patients need pharmacological intervention. The first step is volume repletion with fluid (up to 10 L daily) and salt (up to 10 g daily) supplemented by the mineralocorticoid 9-alpha-fluorohydrocortisone (0·1–0·3 mg daily). A sympathomimetic agent can be added should symptoms persist. Midodrine, a direct, peripherally acting alpha-1-adrenoreceptor agonist, is the most widely used of these pressors. The dose should be titrated from 2·5 mg to 10·0 mg three times a day to limit the risk of an exaggerated pressor response due to denervation supersensitivity.[45] Spallone V et al concluded that Intensive diabetes therapy retards the development of CAN in type 1 diabetes, Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes and Lifestyle intervention may improve HRV in pre-diabetes and diabetes, Symptomatic orthostatic hypotension may be improved by non-pharmacological measures and by midodrine and/or fludrocortisone. Drug treatment of symptomatic orthostatic hypotension in diabetic patients with CAN may be challenging and should be thoroughly balanced between the goal of increasing standing blood pressure and the avoidance of a marked increase in supine blood pressure .[46]

Midodrine is a selective α1-adrenergic agonist that acts peripherally and is considered to be the first line agent that can act through peripheral vasoconstriction of both arterioles and veins. Till date this is the only drug approved by food and drug administration (FDA) for orthostatic hypotension treatment. [47,48]

9-α-fluorohydrocortisone which is a synthetic mineralocorticoid is another first line medication that can act via sodium retention and also plasma expansion. In a double blind crossover study, 9-α-fluorohydrocortisone was used to treat successfully orthostatic hypotension of the patients with diabetes along with autonomic neuropathy. [49]

Somatostatin and its analogues (octreotide) are found to inhibit release of the vasoactive peptides from the gastrointestinal tract and hence increase the splanchnic vasoconstriction, which lead to increase in mean blood pressure. Using long acting octreotide in the patients with autonomic neuropathy was found to have increased the systolic BP from 83.8±7.1 mmHg to 104.1±3.1 mmHg (P value < 0.025) within 8 weeks, with improving orthostatic fatigue and dizziness. [50]

Other pharmacological strategies available include use of erythropoietin that can increase erect BP through increase of RBC mass and also circulating volume with improvement of anemia and its regulatory effect on the vascular tone and desmopressin which is mainly observed in the morning time hypotension. [51]

Unfortunately, despite various different treatment options available, postural hypotension is a difficult condition that can be treated and many of the patients require multiple therapies

THE RENNIN – ANGIOTENSIN – ALDOSTERONE AXIS

There is enough evidence to support use of certain agents in improving left ventricular dysfunction which is associated with autonomic neuropathy among diabetics. In patients who have heart failure, the use of bisoprolol [52] or addition of spironolactone to enalapril, digoxin and furosemide [53], have demonstrated beneficial effect on the autonomic function, as exhibited by HRV testing and also sympatho-vagal balance respectively. Use of angiotensin-converting enzyme (ACE) inhibitors can potentially improve the sympathetic and parasympathetic balance (54) and improve the prognosis in heart failure.[55] The addition of ARBs to ACE inhibitors may be better than monotherapy, due to the increased blockade on renin-angiotensin-aldosterone axis. [56-58]

BrederI SS et al concluded that CAN is a frequent and important diagnosis achieved through the screening test recommended by the ADA. Due to its prognostic importance in DM2, the risk of sudden death and myocardial infarction and the possibility of treatment must not be neglected. [59]

Xubin Yang et al concluded that In conclusion, higher serum CysC was associated with impaired cardiovascular autonomic function, especially the injury to parasympathetic nerve function in type 2 diabetic patients. CysC might be a reliable and convenient biomarker for detecting cardiovascular autonomic dysfunction. [60]

Bijaya K B concluded that cardiac autonomic neuropathy is a common and early complication of DM and it is associated with increased mortality due to cardiovascular related causes. Paucity of related symptoms leads to delayed detection of CAN. Proper history taking to identify symptoms related to CAN and performing simple autonomic tests in all patients of DM can identify cardiac autonomic neuropathy. Our study shows that 57.5% of the cases of diabetes mellitus had cardiac autonomic neuropathy and its incidence increased with severity of hyperglycemia, age and associated nephropathy. [61]

Charles M et al concluded that signs of CAN were highly prevalent in a well-treated population with screen-detected type 2 diabetes. The prevalence of CAN was not reduced by education and support of general practitioners and practice nurses in evidence-based target-driven management and treatment targets/algorithms compared with routine care according to national guidelines, but at follow-up the participants in the two treatment groups were equally well treated. [62]

MATERIALS AND METHODS

The study was conducted in the Department of Medicine, Department of Endocrinology and the Allied Specialities of Medicine, Dayanand Medical College and Hospital, Ludhiana. 100 Type 2 Diabetes Mellitus OPD and indoor patients were enrolled for this study and was conducted over a period of one and a half years.

SOURCE OF DATA

The study was conducted in Department of Medicine, Department of Endocrinology and the Allied specialities of Dayanand Medical College and Hospital, Ludhiana.

METHOD OF COLLECTION OF DATA

Type 2 Diabetes mellitus patients presenting to OPD and IPD who fulfilled the inclusion/exclusion criteria.

INCLUSION CRITERIA

1. Type 2 Diabetes Mellitus patients of age more than 18 years of both sexes
2. Duration of diabetes for at least 1 year
3. Patients who gave informed written consent

EXCLUSION CRITERIA

1. Patients who were on beta blockers
2. Patients who were on drugs that prolong QTc
3. Chronic renal failure
4. History of ischaemic heart disease
5. Anemia (moderate 8-10 g/dl to severe<8 g/dl)
6. Asthma or COPD
7. Those who did not give consent

The relevant history was taken and clinical examination was done. Cardiovascular, respiratory, abdominal and CNS examination (especially to assess the presence of neuropathy by ankle jerk and vibration sense) was done in all subjects.

The basic investigations such as Haemoglobin, HbA1C, serum creatinine, electrolytes, SGPT, lipid profile, urine routine, etc done was recorded.

Tests for assessment of cardiovascular autonomic function were done.

Tests for Parasympathetic function

1. Heart rate response to deep breathing
2. Heart rate response to Valsalva Maneuver (Valsalva ratio)
3. Heart rate response to immediate standing (30: 15 ratio)

Tests for Sympathetic function

1. Blood pressure response to standing
2. Blood pressure response to sustained hand grip

Interpretation of test results

Test results were interpreted as per Ewing's criteria:

Normal = All tests normal or 1 test borderline

Early = One of the three heart rate tests abnormal or two borderline

Definite = Two heart rate tests abnormal

Severe = Two heart rate tests abnormal + one or both BP tests abnormal or both borderline

Atypical= Any other combination of abnormalities

TABLE 2: TESTS FOR ASSESSMENT OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION WERE DONE AS UNDER [3]

Test	Technique	Normal response and value
Beat to Beat HRV	With patient at rest and supine, heart rate is monitored by ECG when patient breathes in and out at 6 breaths/min	A difference in HR of >15 beats/min is normal and <10 beats/min is abnormal .The lowest normal value for expiration to inspiration ratio of R-R interval decreases with age (20-24 yr-1.17,25-29 yr-1.15,30-34-1.13,35-39 yr-1.12,40-44 yr-1.10 ,45-49-1.08,50-54 yr -1.07,55-59 yr-1.06,60-64 yr-1.04,65-69 yr-1.03,70-75 yr-1.02)
Heart Rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03, borderline 1.01-1.03
Heart Rate Response to the Valsalva Maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 secs during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is > 1.2, borderline 1.11-1.2
Systolic blood pressure response to standing	Systolic BP is measured in the supine subject. The patient stands and the systolic BP is measured after 2 min	Normal response is a fall of < 10 mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of > 30 mmHg
Diastolic blood pressure response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic BP is a rise of > 16 mmHg in the other arm, borderline 11-15 mmHg

TABLE 3: INTERPRETATION OF THE CAN TESTS [3]

Interpretation	Normal	Borderline	Abnormal
Tests reflecting mainly parasympathetic function			
Heart rate response to Valsalva Manoeuvre (Valsalva ratio)	≥ 1.21	1.11–1.20	≤ 1.10
Heart rate (R-R interval) variation	≥15 beats/min	11–14 beats/min	≤10 beats/min
Immediate heart rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Tests reflecting mainly sympathetic function			
Blood pressure response to standing (fall in systolic blood mm Hg of pressure)	≤10 mmHg	11–29 mmHg	≥ 30 mmHg
Blood pressure response to sustained handgrip (increase in diastolic blood pressure)	≥16 mmHg	11–15 mmHg	≤ 10 mmHg

PICTURE 1: ECG MACHINE

PICTURE 2: HAND HELD DYNAMOMETER

STATISTICAL ANALYSIS

Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. Receiver operator characteristics (ROC) curve was done, and criterion value was estimated depending on the specificity and sensitivity. Area under curve (AUC) was measured. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

The study was conducted in the Department of Medicine, Department of Endocrinology and the Allied Specialities of Medicine, Dayanand Medical College and Hospital, Ludhiana. 100 Type 2 Diabetes Mellitus patients were enrolled for this study.

TABLE 4: AGE WISE DISTRIBUTION OF CASES IN THE STUDY GROUP

Age GROUP(IN YEARS)	No. of cases	Percentage
< 40	6	6.0%
41-50	24	24.0%
51-60	33	33.0%
61-70	27	27.0%
71-80	10	10.0%
Total	**100**	**100.0%**

In our study, maximum of 33 patients (33%) were in age group 51-60 years. The mean age of our study population was 56.57±11.86 years.

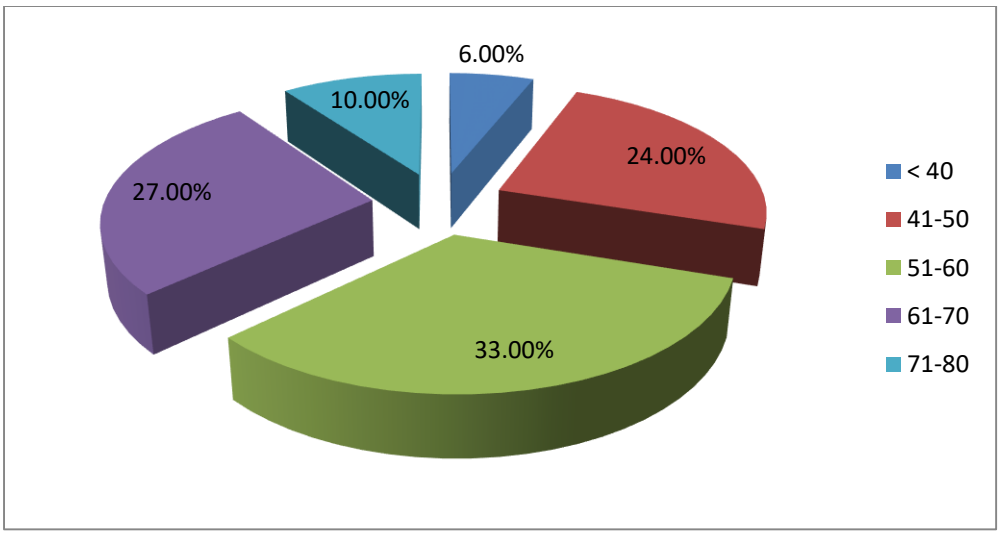

FIGURE 3: AGE WISE DISTRIBUTION OF CASES IN THE STUDY GROUP

TABLE 5: SEX WISE DISTRIBUTION OF CASES IN THE STUDY GROUP

Gender	No. of cases	Percentage
Males	59	59.0%
Females	41	41.0%
Total	**100**	**100.0%**

Out of 100 patients 59 (59%) were males and 41 (41%) were females.

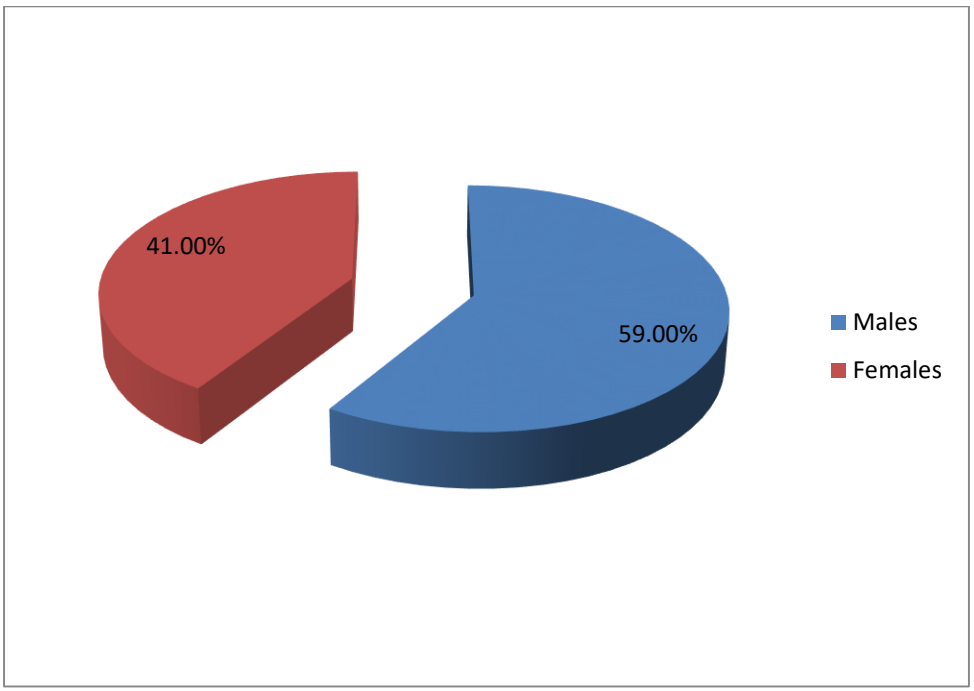

FIGURE 4: SEX WISE DISTRIBUTION OF CASES IN THE STUDY GROUP

TABLE 6: DURATION OF DIABETES

Duration of Diabetes	No. of cases	Percentage
< 5 years	22	22.0%
5-10 years	52	52.0%
> 10 years	26	26.0%
Total	100	100.0%

Out of total 100 patients, duration of diabetes was less than 5 years in 22(22%), 5-10 years in 52(52%) and greater than 10 years in 26(26%) patients. The mean duration of diabetes in our study population was 8.83 ± 5.55 years.

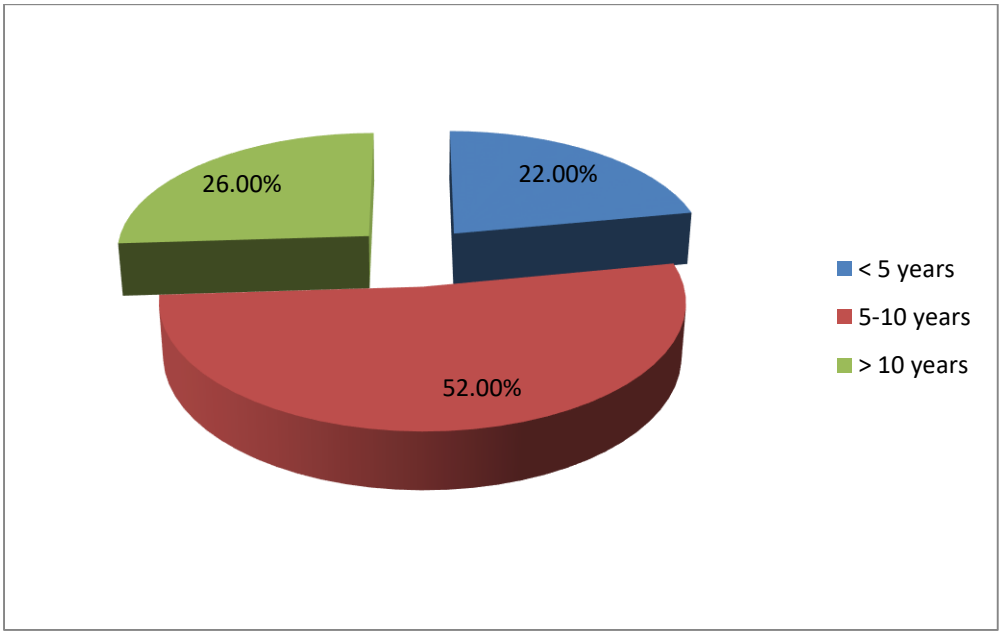

FIGURE 5: DURATION OF DIABETES

TABLE 7: TREATMENT HISTORY

Treatment History	No. of cases	Percentage
Insulin	25	25.0%
OHA's	61	61.0%
Not on Any Treatment	14	14.0%
Total	**100**	**100.0%**

Out of total 100 patients, 61(61 %) patients were on OHAS, 25(25%) patients were on Insulin and 14(14%) were not on any treatment.

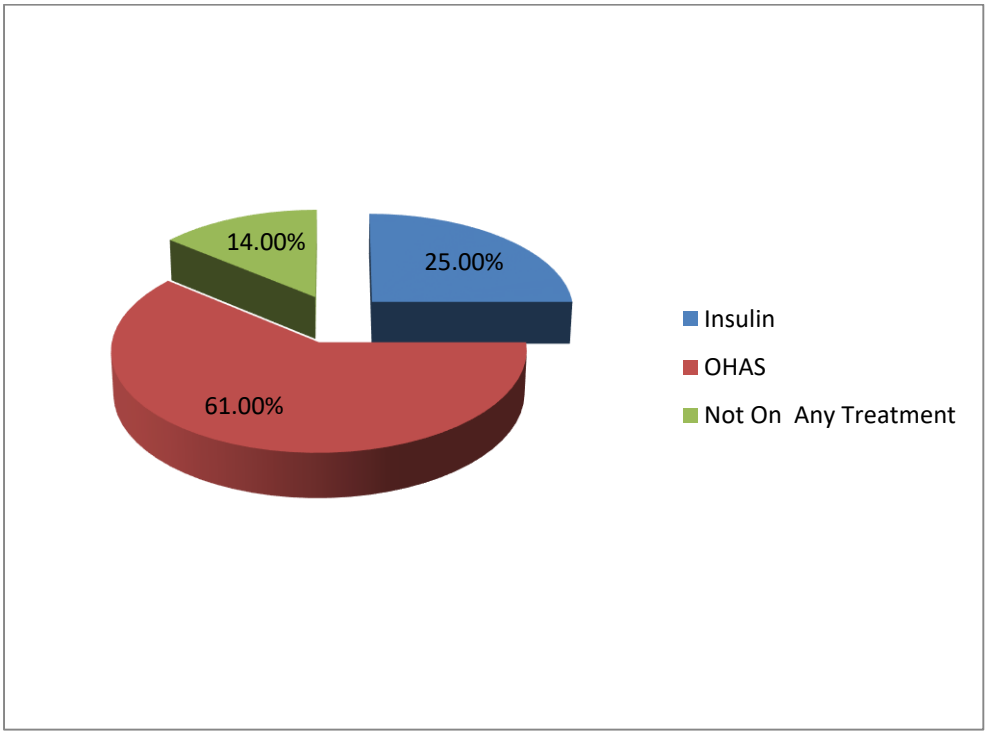

FIGURE 6: TREATMENT HISTORY

TABLE 8: HISTORY OF PRESENT ILLNESS

History of Present Illness	No. of cases	Percentage
1.Tingling/Burning Sensation/ Numbness/ Sharp Jabbing Pain/Loss of sensation	50	50.0%
2. Facial Puffiness ,Pedal Edema	16	16.0%
3. Visual Complaints	10	10.0%
4. Chest Pain on Exertion	1	1.0%
5. Dyspnea on Exertion	9	9.0%

In our study maximum patients i.e 50% complained of tingling, burning sensation, numbness, sharp jabbing pain or loss of sensation.

TABLE 9: CO-EXISTING MORBIDITIES

Co-Existing Morbidities	No. of cases	Percentage
Hypertension	62	62.0%
Hypothyroidism	2	2.0%

Out of 100 diabetic patients in our study, 62(62%) had hypertension and 2(2%) had hypothyroidism.

TABLE 10: PRESENCE OF DIABETIC NEUROPATHY IN THE STUDY GROUP

CNS	No. of cases	Percentage
Diabetic Neuropathy Present	33	33.0%
Diabetic Neuropathy Absent	67	67.0%
Total	**100**	**100.0%**

Out of 100 patients in our study 33(33%) patients had diabetic neuropathy on neurological examination

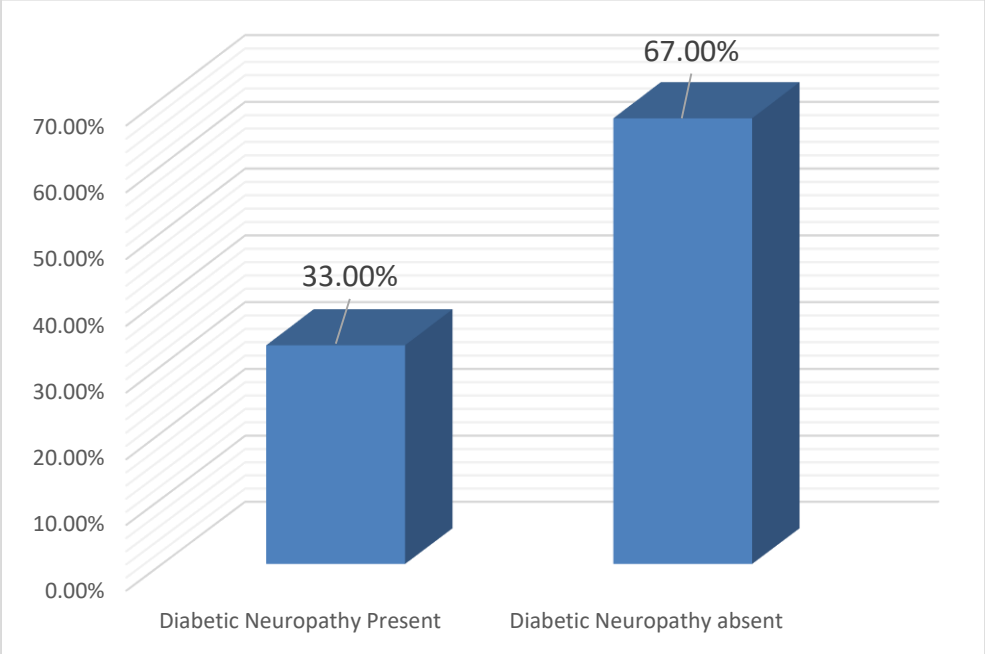

FIGURE 7: PRESENCE OF DIABETIC NEUROPATHY IN THE STUDY GROUP

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TABLE 11: PRESENCE OF ALBUMINURIA IN THE STUDY GROUP

Urine Albumin	No. of cases	Percentage
Traces	2	2.0%
1+	38	38.0%
2+	16	16.0%
3+	10	10.0%
Total Cases with Albuminuria	66	66.0%
Nil	34	34.0%
Total	**100**	**100.0%**

Out of 100 patients, 66 (66%) patients had albuminuria and 34 (34%) did not have albuminuria. 2 (2%) had urine albumin in traces; 38 (38%) had 1+ albuminuria; 16(16%) had 2+ albuminuria and 10 (10%) had 3+ albuminuria.

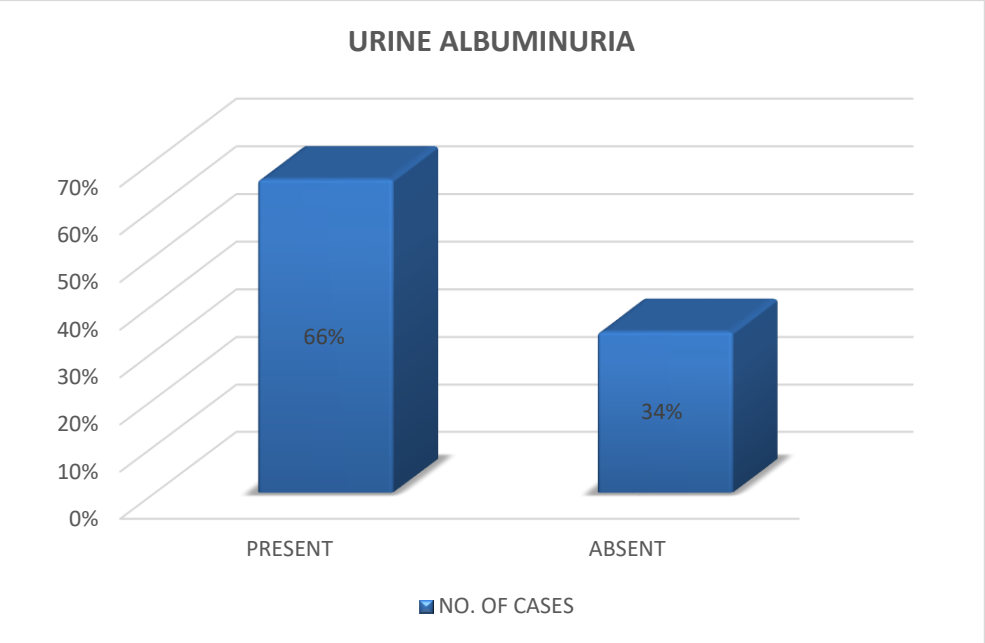

FIGURE 8: PRESENCE OF ALBUMINURIA IN THE STUDY GROUP

TABLE 12: PRESENCE OF URINE GLYCOSURIA IN THE STUDY GROUP

Urine Glucose	No. of cases	Percentage
Present	34	34.0%
Absent	66	66.0%

Out of 100 patients, 34(34%) patients had urine glycosuria.

TABLE 13: PRESENCE OF DIABETIC RETINOPATHY IN THE STUDY GROUP

Fundus Examination	No. of cases	Percentage
Mild NPDR	13	32.5%
Severe NPDR	3	7.5%
Total Diabetic Retinopathy	16	40.0%
Normal	24	60.0%
Total	**40**	**100.0%**

In our study, fundus examination was done in 40 patients out of which 13 (32.5%) patients had mild NPDR and 3 (7.5%) had severe NPDR. Out of 40 patients, 24 (60%) had normal fundus examination. So diabetic retinopathy was present in 16(40%) patients in whom fundus was done.

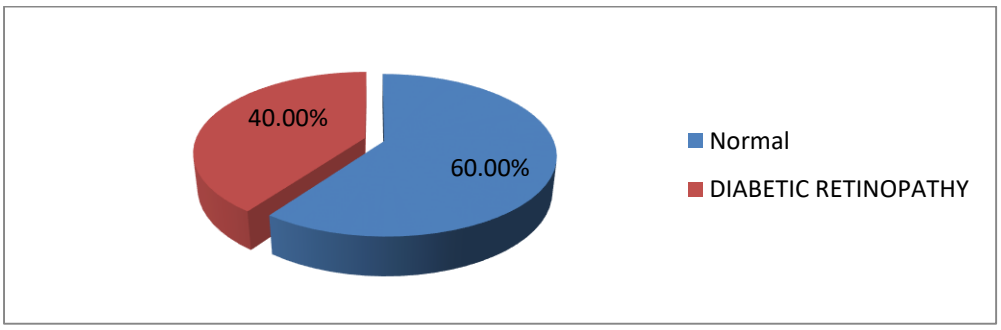

FIGURE 9: PRESENCE OF DIABETIC RETINOPATHY IN THE STUDY GROUP

TABLE 14: HbA1C DISTRIBUTION IN THE STUDY GROUP

HbA1C	No. of Cases
5 - 7.5%	16
7.5 – 10%	67
>10%	17
TOTAL	**100**

Out of 100 patients, 17(17%) had HbA1c > 10, 67(67%) had HbA1c of 7.5-10 and 16(16%) had HbA1c of 5-7.5. Maximum patients were having HbA1c of 7.5-10. The mean HbA1c in our study population was 8.95±1.39%.

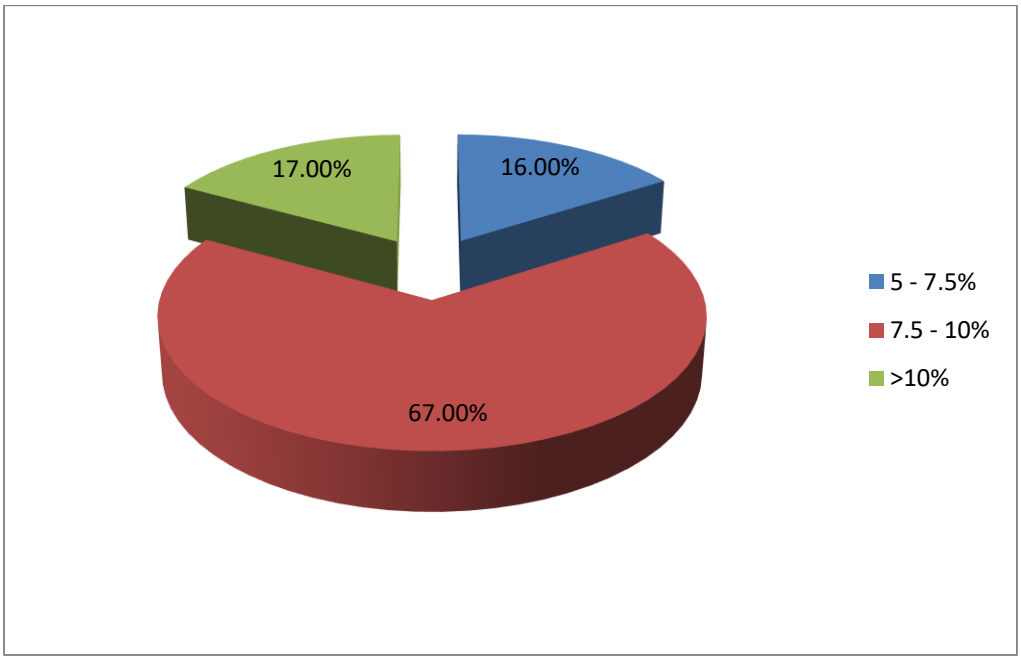

FIGURE 10: HbA1C DISTRIBUTION IN THE STUDY GROUP

CARDIAC AUTONOMIC NEUROPATHY

In our study, tests for assessment of cardiovascular autonomic neuropathy were done which consisted of 3 parasympathetic tests and 2 sympathetic tests. Results were interpreted as per Ewing's Criteria.

RESULTS OF PARASYMPATHETIC TESTING

TABLE 15: HEART RATE RESPONSE TO VALSALVA MANOEUVRE INTERPRETATION

1. Heart Rate Response to Valsalva Manoeuvre	No. of cases	Percentage
Abnormal	29	29.0%
Borderline	16	16.0%
Normal	55	55.0%
Total	**100**	**100.0%**

Out of 100 patients, 29(29%) had abnormal response, 16(16%) had borderline response and 55(55%) had normal test results.

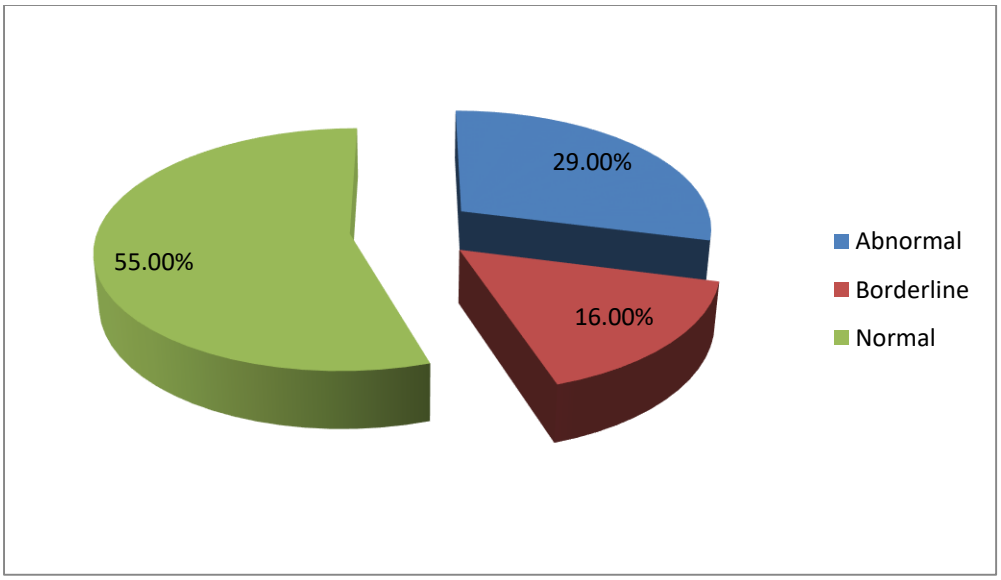

FIGURE 11: HEART RATE RESPONSE TO VALSALVA MANOEUVRE INTERPRETATION

TABLE 16: HEART RATE RESPONSE TO STANDING INTERPRETATION

2. Heart Rate Response to standing	No. of cases	Percentage
Abnormal	11	11.0%
Borderline	17	17.0%
Normal	72	72.0%
Total	**100**	**100.0%**

Out of 100 patients, 11(11%) had abnormal response, 17(17%) had borderline response and 72(72%) had normal test results.

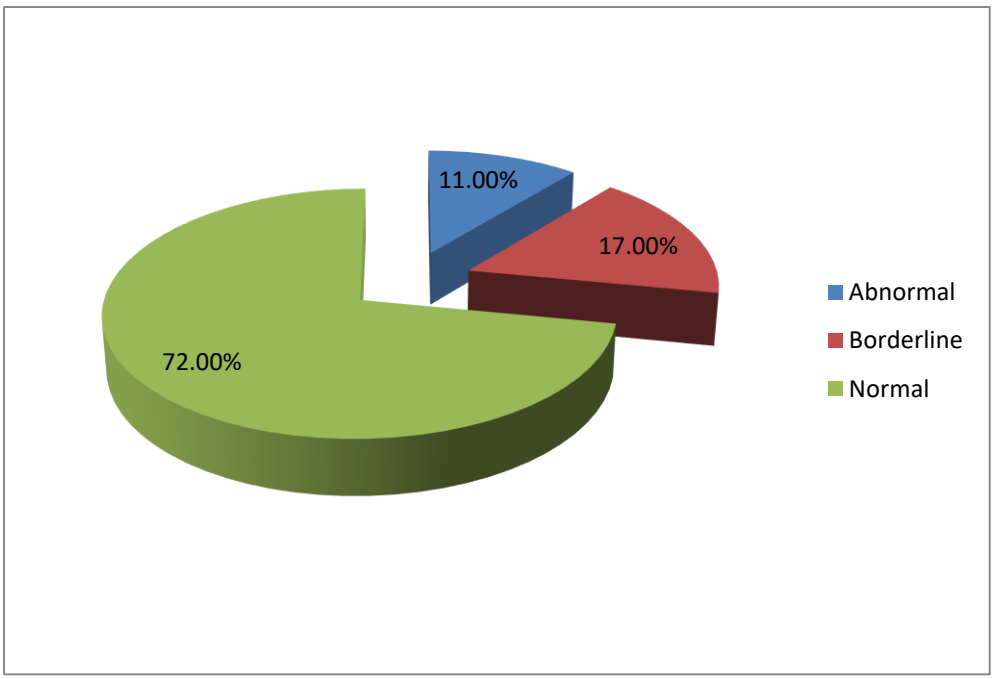

FIGURE 12: HEART RATE RESPONSE TO STANDING INTERPRETATION

TABLE 17: HEART RATE RESPONSE TO DEEP BREATHING INTERPRETATION

3. HEART RATE RESPONSE TO DEEP BREATHING	No. of cases	Percentage
Abnormal	35	35.0%
Borderline	20	20.0%
Normal	45	45.0%
Total	**100**	**100.0%**

Out of 100 patients, 35(35%) had abnormal response, 20(20%) had borderline response and 45(45%) had normal test results.

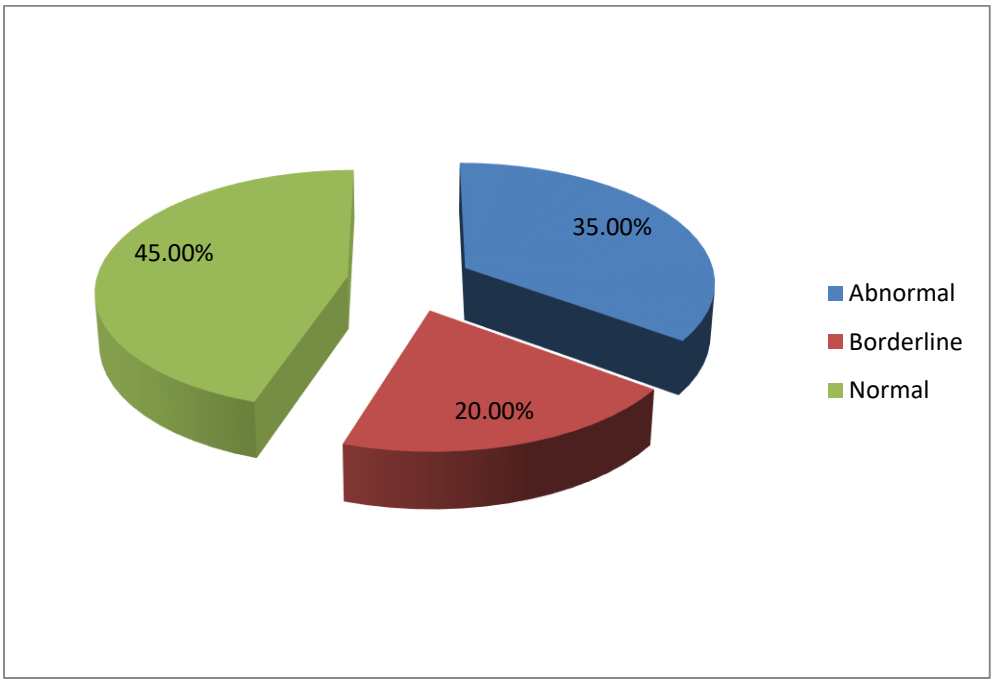

FIGURE 13: HEART RATE RESPONSE TO DEEP BREATHING INTERPRETATION

RESULTS OF SYMPATHETIC TESTING

TABLE 18: BP RESPONSE TO STANDING (FALL IN SYSTOLIC BP) INTERPRETATION

4. BP RESPONSE TO STANDING (FALL IN SYSTOLIC BP)	No. of cases	Percentage
Abnormal	9	9.0%
Borderline	31	31.0%
Normal	60	60.0%
Total	100	100.0%

Out of 100 patients, 9(9%) had abnormal response, 31(31%) had borderline response and 60(60%) had normal test results.

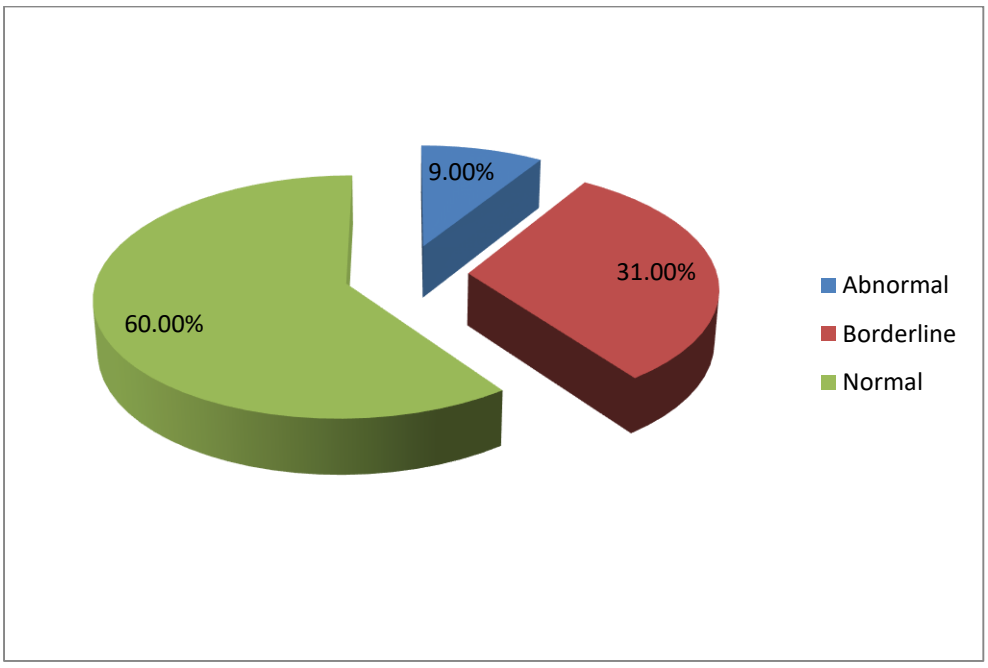

FIGURE 14: BP RESPONSE TO STANDING (FALL IN SYSTOLIC BP) INTERPRETATION

TABLE 19: BP RESPONSE TO SUSTAINED HAND GRIP INTERPRETATION

5. BP RESPONSE TO SUSTAINED HAND GRIP	No. of cases	Percentage
Abnormal	10	10.0%
Borderline	32	32.0%
Normal	58	58.0%
Total	**100**	**100.0%**

Out of 100 patients, 10 (10%) had abnormal response, 32 (32%) had borderline response and 58 (58%) had normal response.

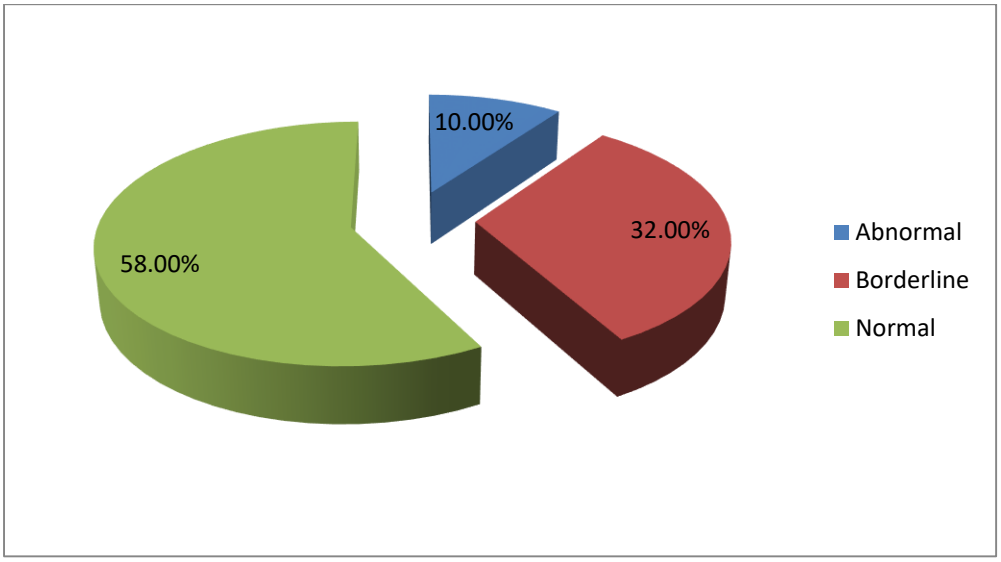

FIGURE 15: BP RESPONSE TO SUSTAINED HAND GRIP INTERPRETATION

So, maximum abnormal response was found in heart response to deep breathing seen in 35 patients (35%) followed by heart rate response to valsalva manoeuvre seen in 29 patients (29 %).

Abnormal heart rate response to standing was seen in 11 patients (11%) followed by BP response to sustained hand grip in 10 patients (10%) and BP response to standing was seen in 9 patients (9%).

RESULTS OF CARDIAC AUTONOMIC NEUROPATHY TESTING

TABLE 20: PREVALENCE OF CAN

CAN	No. of cases	Percentage
Present	67	67.0%
Absent	33	33.0%

Out of 100 diabetic patients studied 67(67%) had presence of CAN and 33(33%) were negative for CAN.

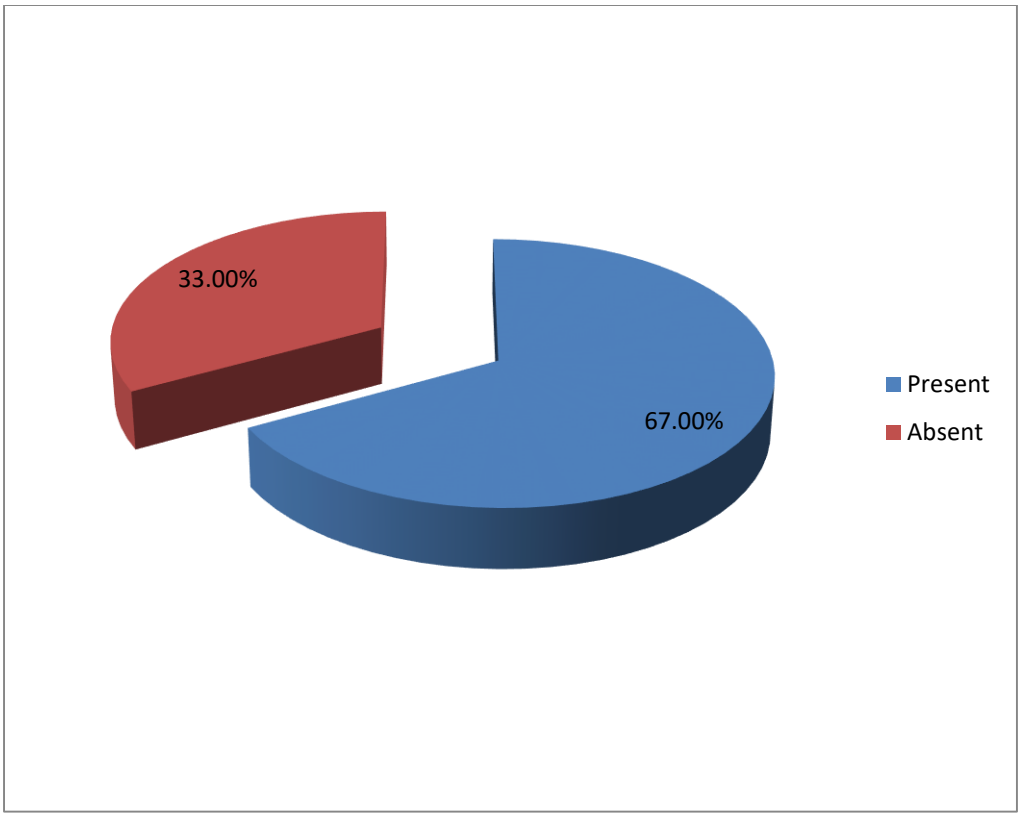

FIGURE 16: PREVALENCE OF CAN

TABLE 21: CLASSIFICATION OF CAN ACCORDING TO EWING'S CRITERIA

INTERPRETATION OF THE RESULTS (According to Ewing's criteria)	No. of cases	Percentage
Early	22	22.0%
Definite	9	9.0%
Severe	18	18.0%
Atypical	18	18.0%
Normal	33	33.0%
Total	100	100.0%

Out of 100 diabetic patients studied, 22(22%) had Early CAN, 9(9%) had Definite CAN, 18(18%) had Severe CAN, 18(18%) had Atypical CAN and 33(33%) had normal results.

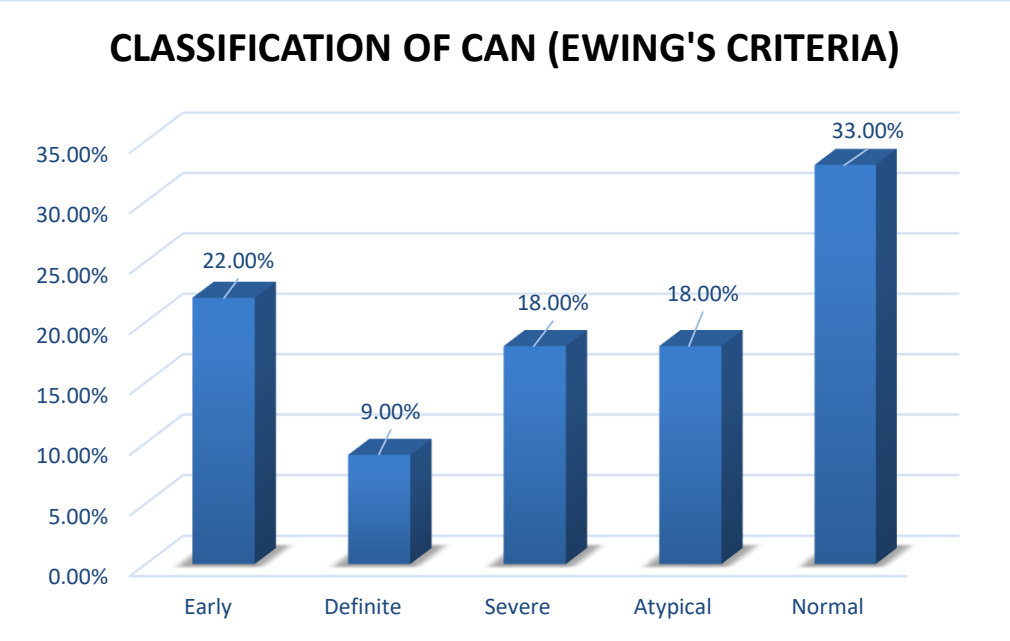

FIGURE 17: CLASSIFICATION OF CAN ACCORDING TO EWING'S CRITERIA

TABLE 22.1: PATTERN OF AUTONOMIC DYSFUNCTION

PATTERN	No. of cases	Percentage
Parasympathetic Alone	30	30.0%
Sympathetic Alone	8	8.0%
Parasympathetic+ Sympathetic	29	29.0%
Normal	33	33.0%
Total	**100**	**100.0%**

TABLE NO 22.2: PATTERN OF AUTONOMIC INVOLVEMENT

PATTERN	No. of cases	Percentage
Total Parasympathetic	59	59.0%
Total Sympathetic	37	37.0%

Out of 67 patients with CAN+, 30(30%) had parasympathetic involvement alone and 8(8%) had sympathetic involvement alone. Both parasympathetic and sympathetic dysfunction was seen in 29(29%) patients. Parasympathetic testing was positive in 59 patients (59%) and sympathetic testing was positive in 37 patients (37%)

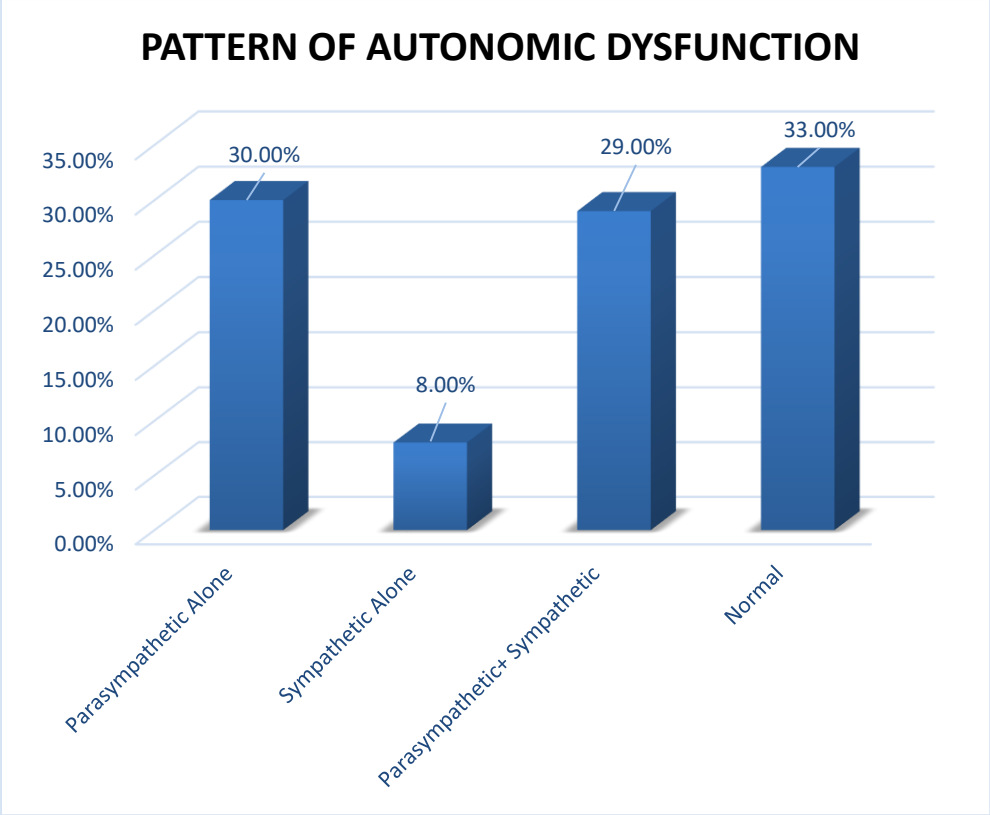

FIGURE 18: PATTERN OF AUTONOMIC DYSFUNCTION

COMPARISON OF VARIOUS PARAMETERS AMONG THE CAN+ AND CAN- GROUP.

TABLE 23.1: COMPARISION OF AGE IN CAN + AND CAN - GROUPS

Comparison	CAN Absent		CAN Present		p-value
	Mean	SD	Mean	SD	
Age (in years)	49.82	12.61	59.90	10.00	0.000

TABLE 23.2: CORRELATION OF AGE WITH PRESENCE OF CAN

		INTERPRETATION OF THE RESULTS (According to Ewing's criteria)				Total	Chi-squar value	p-value
		CAN Absent		CAN Present				
Age GROUP (in years)	< 50	18	54.5 %	12	17.9%	30	14.131	0.0001
	> 50	15	45.5 %	55	82.1%	70		
Total		33	100.0%	67	100.0 %	100		

Mean age was greater in CAN+ group as compared to CAN- group (59.90±10.0 versus 49.82±12.61). It was observed that at age >50 years presence of CAN was 82.1% as compared to age <50 years where presence of CAN was seen in 17.9%. Increasing age had statistically significant (p value-0.000) correlation with presence of CAN.

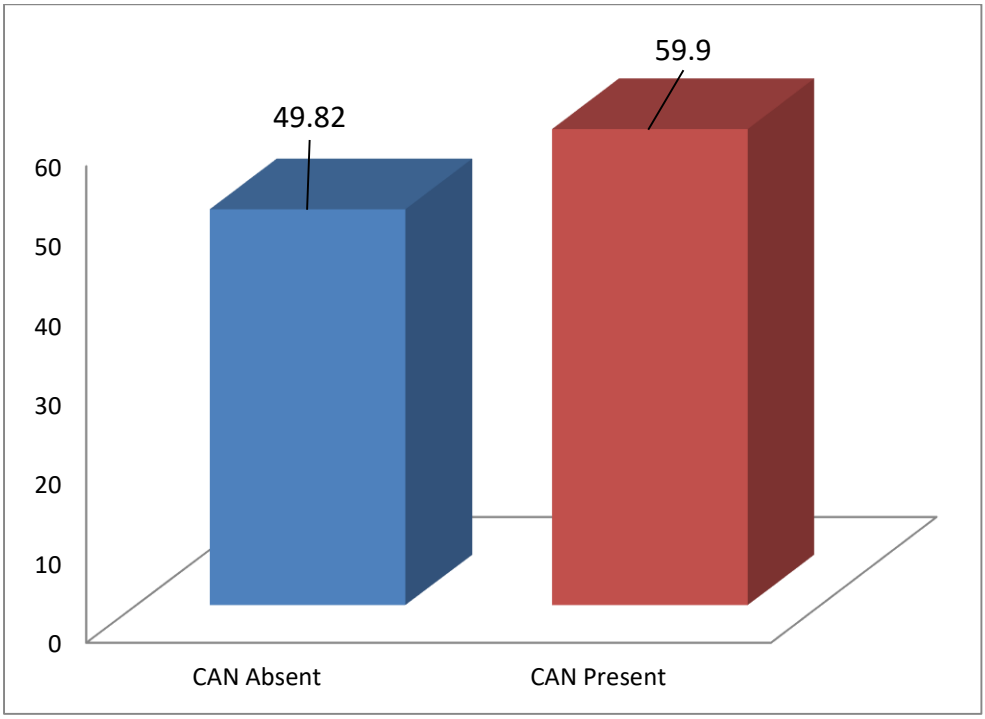

FIGURE 19: COMPARISION OF AGE IN CAN + AND CAN - GROUPS

TABLE 24: CORRELATION OF GENDER WITH PRESENCE OF CAN

		INTERPRETATION OF THE RESULTS (According to Ewing's criteria)				Total	Chi-square value	p-value
		CAN Absent		CAN Present				
Gender	Female	13	39.4 %	28	41.8 %	41	0.053	0.819
	Male	20	60.6 %	39	58.2 %	59		
Total		33	100.0 %	67	100. 0%	100		

Gender did not have any statistical significant correlation with presence of CAN.

TABLE 25.1: COMPARISION OF DURATION OF DIABETES IN CAN + AND CAN- GROUPS

	Absent		**Present**		p-value
	Mean	**SD**	**Mean**	**SD**	
Duration of Diabetes (in years)	5.23	3.18	10.60	5.62	0.000

Duration of diabetes was greater in CAN+ group as compared to CAN- group (mean duration- 10.60±5.62 versus 5.23±3.18) and increasing duration of diabetes had statistically significant (p value-0.000) correlation with presence of CAN.

TABLE 25.2: CORRELATION OF DURATION OF DIABETES WITH THE PRESENCE OF CAN

		INTERPRETATION OF THE RESULTS (According to Ewing's criteria)				Total	Chi-squar value	p-value
		CAN Absent		CAN Present				
Duration of Diabetes group	<5 years	15	45.5 %	7	10.4%	22	22.313	0.0001
	5-10 years	17	51.5 %	35	52.2%	52		
	>10 years	1	3.0%	25	37.3%	26		
Total		33	100.0 %	67	100.0 %	100		

With duration of diabetes <5 years, 7 out of 22 subjects were positive for CAN, with duration 5-10 years, 39 out of 59 subjects were positive for CAN and with duration >10 years, 25 out of 26 subjects were positive for CAN. This was statistically significant. (p value-0.0001)

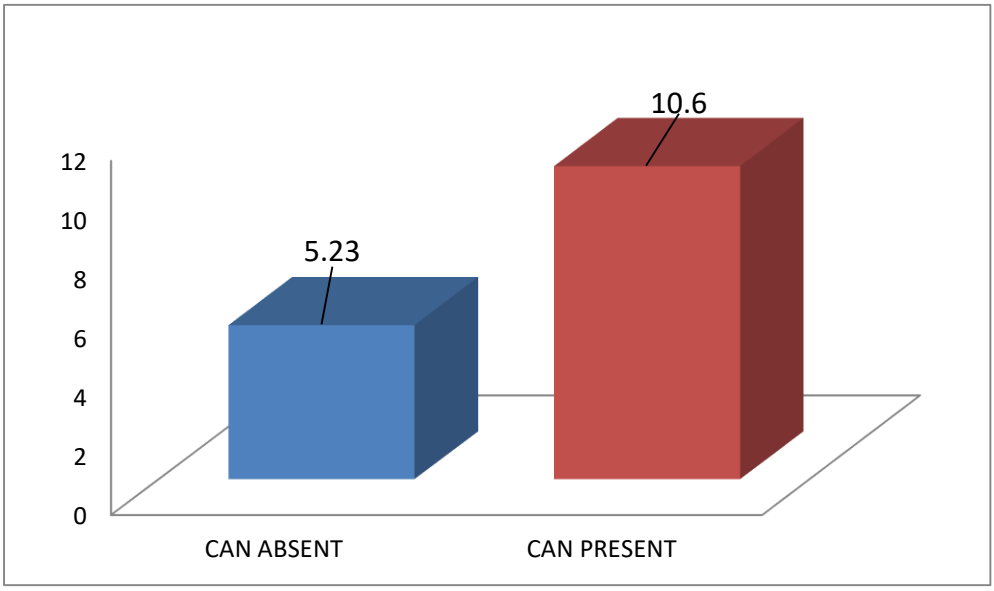

FIGURE 20: COMPARISION OF DURATION OF DIABETES IN CAN + AND CAN - GROUPS

TABLE 26: HEART RATE AND BLOOD PRESSURE COMPARED IN PATIENTS WITH CAN + AND CAN - GROUPS

	CAN Absent		CAN Present		p-value
	Mean	**SD**	**Mean**	**SD**	
Heart Rate	87.52	9.01	87.61	8.19	0.957
SBP (mm Hg)	116.36	6.03	121.19	8.08	0.003
DBP (mm Hg)	75.76	5.02	78.21	5.20	0.027

SBP (p value-0.003) and DBP (p value-0.027) had statistically significant correlation with presence of CAN with mean SBP and DBP being statistically higher in CAN+ group.

There was no statistical difference in the heart rate between CAN+ and CAN-groups.

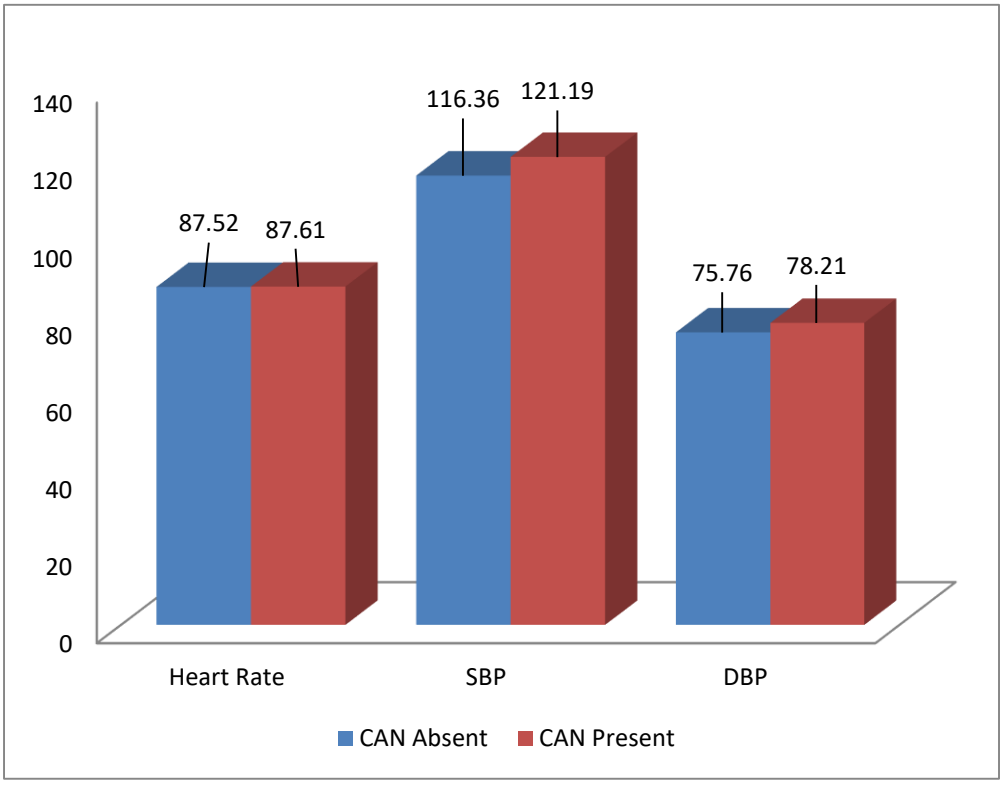

FIGURE 21: COMPARISION OF HEART RATE AND BLOOD PRESSURE IN CAN + AND CAN – GROUPS

TABLE 27: LAB PARAMETERS COMPARED IN CAN + AND CAN - GROUPS

LAB PARAMETERS	CAN Absent		CAN Present		p-value
	Mean	SD	Mean	SD	
Hemoglobin (g/dL)	11.68	1.50	11.56	1.39	0.714
Serum Creatinine (mg/dL)	0.67	0.19	0.82	0.24	0.002
Sodium (meq/L)	137.0	4.70	135.37	4.00	0.075
Potassium (meq/L)	4.06	0.33	4.22	0.37	0.039
Chloride (meq/L)	99.39	3.47	100.45	4.29	0.223
SGPT (IU/L)	60.45	95.24	50.10	81.24	0.573

Out of the lab parameters, serum creatinine (p value-0.002) was higher in CAN+ than in CAN- patients and correlation was statistically significant. Serum potassium (p value-0.039) also had statistically significant relationship with higher serum potassium in CAN+ group. Rest of the lab parameters that is haemoglobin, serum sodium, serum chloride and SGPT were not found to have any statistical correlation with presence of CAN.

TABLE 28: LIPID PROFILE COMPARED IN CAN + AND CAN - GROUPS

	CAN Absent		CAN Present		p-value
	Mean	SD	Mean	SD	
LDL	87.95	34.64	94.27	32.60	0.469
HDL	37.19	12.87	37.71	13.17	0.878
Triglycerides	153.90	41.62	158.41	33.07	0.631
Cholesterol	204.14	49.03	197.47	46.18	0.588

LDL, HDL, triglycerides and cholesterol were found to have no statistical correlation with presence of CAN.

TABLE NO 29.1: HbA1c COMPARED IN CAN + AND CAN - GROUPS

	CAN Absent		**CAN Present**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
HbA1c (%)	8.71	1.68	9.07	1.21	0.221

TABLE NO 29.2: CORRELATION OF HbA1c WITH PRESENCE OF CAN

		Interpretation Of The Results (According To Ewing's Criteria)				Total	Chi-squar value	p-value
		CAN Absent		CAN Present				
HbA1c (%)	5-7.5	7	21.2%	9	13.4 %	16	1.527	0.466
	7.5-10.0	22	66.7%	45	67.2 %	67		
	> 10	4	12.1%	13	19.4 %	17		
Total		33	100%	67	100%	100		

There were 16 patients with HbA1c of 5-7.5, 9 (13.4%) had CAN+ and 7 (21.2%) had CAN- . 67 patients had HbA1C of 7.5-10, 45 (67.2%) had CAN+ and 22 (66.7%) had CAN- . 17 patients had HbA1C >10, 13 (19.4%) had CAN+ and 4 (12.1%) had CAN-.

Mean HbA1c was found higher in CAN+ as compared to CAN- group (mean HbA1c 9.07±1.21 versus 8.71±1.68). However HbA1c had no statistical significant correlation with presence of CAN.

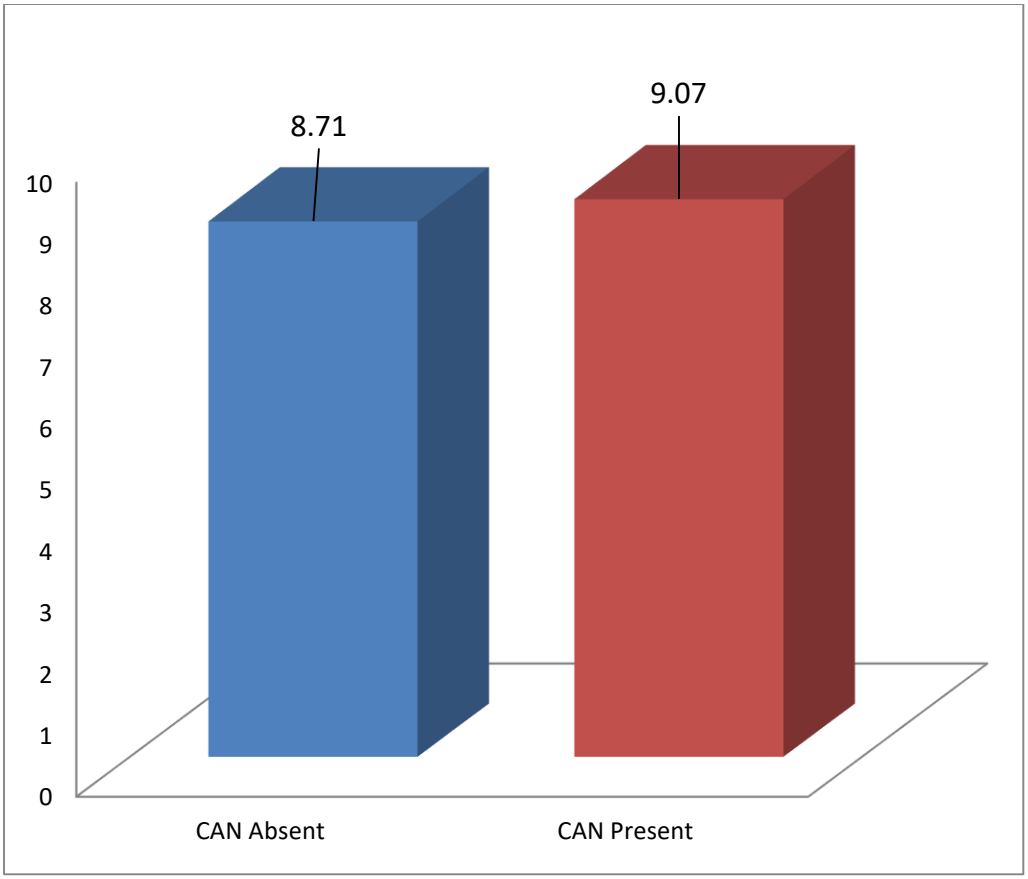

FIGURE 22: COMPARISION OF HbA1c IN CAN + AND CAN - PATIENTS

TABLE 30: CORRELATION OF ERECTILE DYSFUNCTION WITH CAN

	Interpretation Of The Results (According To Ewing's Criteria)					Total	Chi-squar value	p-value
	CAN Absent			CAN Present				
Erectile Dysfunction	Yes	1	5.0%	10	25.6%	11	3.713	0.079
	No	19	95.0%	29	74.4%	48		
Total		20	100.0 %	39	100.0%	59		

Out of 59 males in the study, 11(18.6%) had erectile dysfunction. Erectile dysfunction was present in 10 patients (25.6%) out of 39 patients who had CAN+ compared to 1 patient (5%) out of 20 patients with CAN-. Thus, erectile dysfunction was seen more in diabetics with CAN as compared to diabetics without CAN.

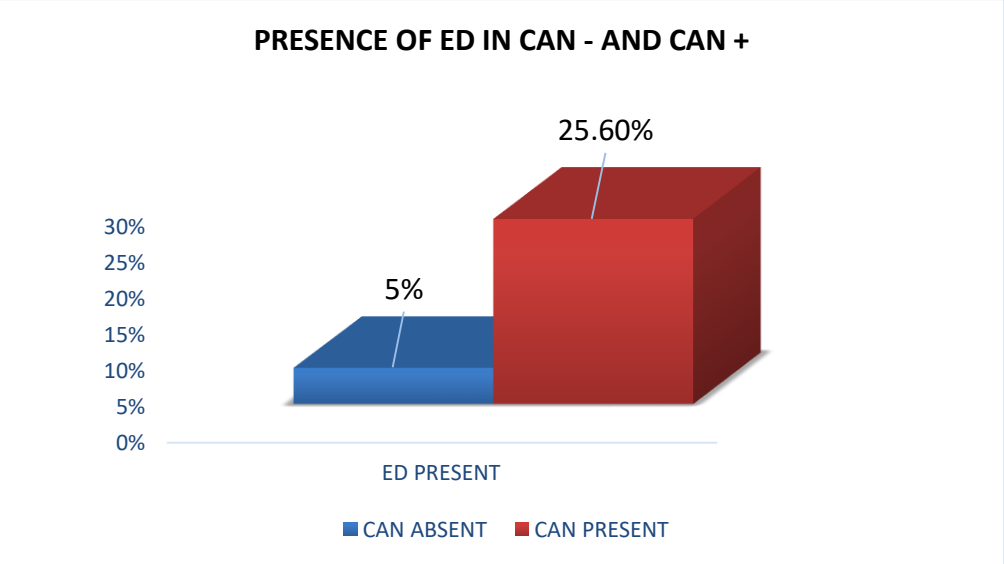

FIGURE 23: COMPARISION OF ERECTILE DYSFUNCTION IN CAN- AND CAN+ GROUPS

TABLE 31: TYPE OF CAN IN ED PATIENTS

TYPE OF CAN	NUMBER OF ED PATIENTS
Early	1(9.09%)
Definite	3(27.27%)
Severe	5(45.45%)
Atypical	1(9.09%)
Normal	1(9.09%)
TOTAL	**11(100%)**

So, severe CAN was present in 5(45.45%) patients of patients with erectile dysfunction.

TABLE 32: CORRELATION OF DIABETIC NEUROPATHY WITH CAN

		Interpretation Of The Results (According To Ewing's Criteria)				Total	Chi-squar value	p-value
		CAN Absent		CAN Present				
CNS	Diabetic Neuropathy Present	6	18.2%	27	40.3%	33	4.8915	0.0269
	Diabetic Neuropathy Absent	27	81.8%	40	59.7%	67		
Total		33	100%	67	100%	100		

In our study, 33(33%) patients had diabetic neuropathy. Diabetic neuropathy was present in 27 patients (40.3%) out of 67 patients who had CAN+ as compared to 6 patients (18.2%) out of 33 patients who had CAN- and this correlation was statistically significant.

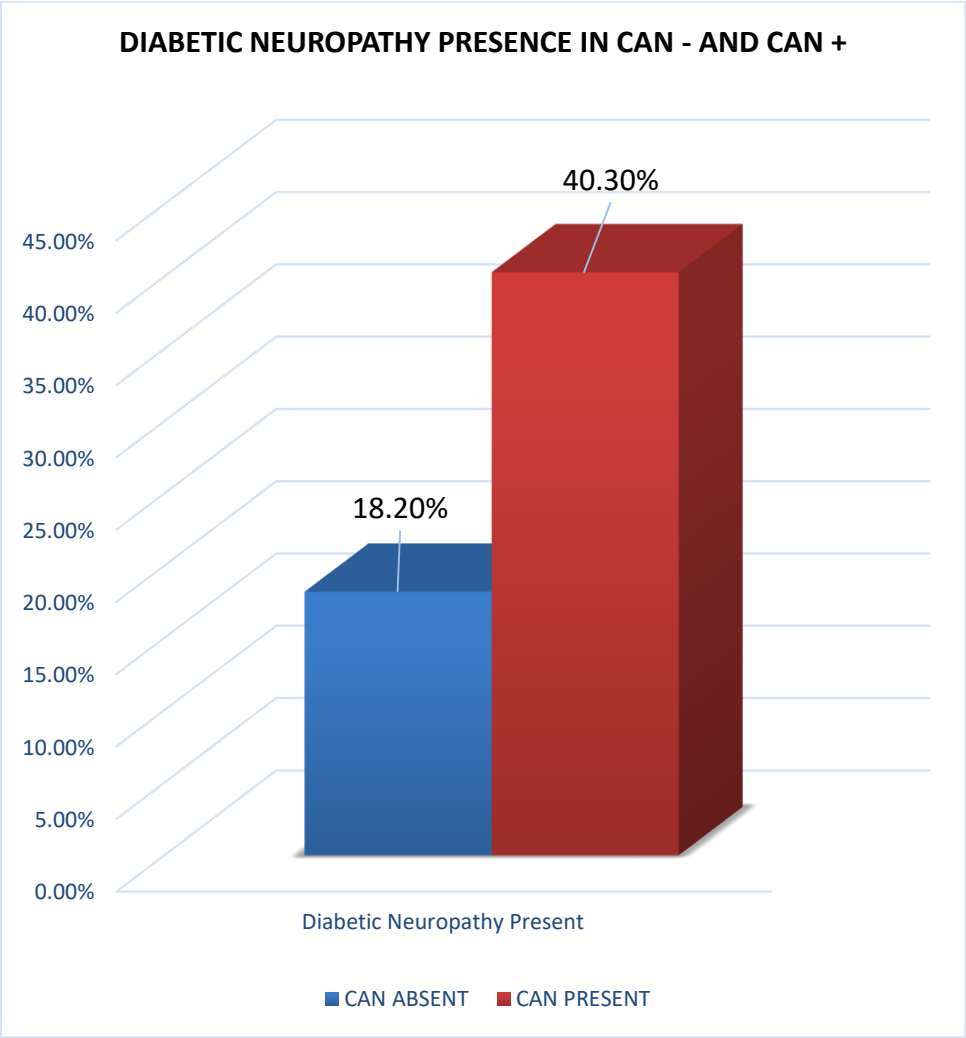

FIGURE 24: COMPARISION OF DIABETIC NEUROPATHY IN CAN- AND CAN+ GROUPS

TABLE 33: CORRELATION OF URINE ALBUMINURIA WITH CAN

		Interpretation Of The Results (According To Ewing's Criteria)				Total	Chi-squar value	p-value
		CAN Absent		CAN Present				
Urine Albumin	Yes	17	51.5%	49	73.1%	66	4.605	0.032
	No	16	48.5%	18	26.9%	34		
	Total	33	100.0 %	67	100.0 %	100		

In our study, 66 patients had urine albuminuria. Urine albuminuria was seen in 49 patients (73.1%) out of 67 patients who had CAN+ as compared to 17 patients (51.5%) out of 33 patients who had CAN- and this correlation was statistically significant.

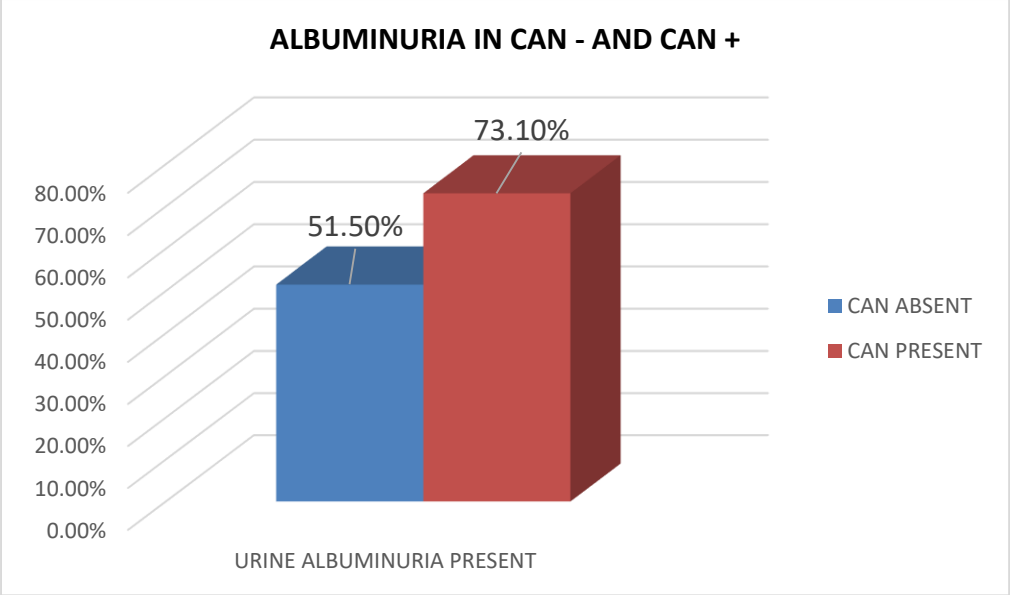

FIGURE 25: COMPARISION OF ALBUMINURIA IN CAN- AND CAN+ GROUPS

TABLE 34: CORRELATION OF DIABETIC RETINOPATHY AND CAN

		Interpretation Of The Results (According To Ewing's Criteria)				Total	Chi-square value	p-value
		CAN Absent		CAN Present				
Diabetic retinopathy (Fundus examination)	Present	4	25%	12	50.0%	16	2.5	0.1138
	Absent	12	75%	12	50.0%	24		
Total		16	100%	24	100.0 %	40		

In our study, 40 patients had fundus examination done out of which 16 had diabetic retinopathy. Diabetic retinopathy was seen in 12 patients (50%) out of 24 patients who had CAN+ as compared to 4 patients (25%) out of 16 patients who had CAN- . Diabetic retinopathy was more in CAN+ group as compared to CAN- group. However, this correlation was not statistically significant.

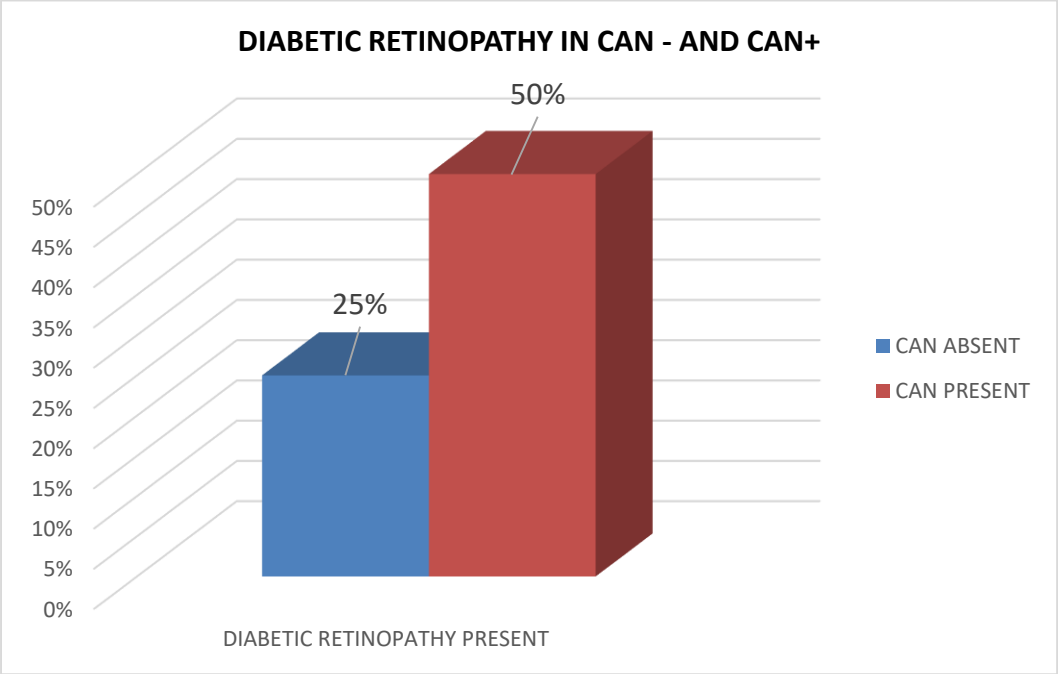

FIGURE 26: COMPARISION OF DIABETIC RETINOPATHY IN CAN- AND CAN+ GROUPS.

TABLE 35: STATISTICAL ANALYSIS OF CAN TESTING

TESTS	1 HEART RATE RESPONSE TO VALSALVA		2 HEART RATE RESPONSE TO STANDING		3 HEART RATE REPONSE TO DEEP BREATHING		4 BP RESPONSE TO STANDING		5 BP RESPONSE TO SUSTAINED HAND GRIP	
Statistics	**Value**	95% CI	**Value**	95% CI	**Value**	95% CI	**Value**	95% CI	**Value**	95% CI
Sensitivity	**61.19%**	48.50% to 72.86%	**32.84%**	21.85% to 45.40%	**79.10%**	67.43% to 88.08%	**53.73%**	41.12% to 66.00%	**63.16%**	49.34% to 75.55%
Specificity	**87.88%**	71.80% to 96.60%	**81.82%**	64.54% to 93.02%	**93.94%**	79.77% to 99.26%	**87.88%**	71.80% to 96.60%	**81.82%**	64.54% to 93.02%
Positive Predictive Value (*)	**91.11%**	80.04% to 96.32%	**78.57%**	62.21% to 89.09%	**96.36%**	87.31% to 99.03%	**90.00%**	77.77% to 95.86%	**85.71%**	73.91% to 92.70%
Negative Predictive Value (*)	**52.73%**	44.59% to 60.72%	**37.50%**	32.24% to 43.08%	**68.89%**	57.96% to 78.05%	**48.33%**	41.24% to 55.50%	**56.25%**	46.89% to 65.19%
Accuracy (*)	**70.00%**	60.02% to 78.76%	**49.00%**	38.86% to 59.20%	**84.00%**	75.32% to 90.57%	**65.00%**	54.82% to 74.27%	**70.00%**	59.43% to 79.21%

We assessed the performance of the individual tests against the total presence of CAN in our study. We calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy of all CAN tests.

In our study Heart rate response to deep breathing was the most sensitive test (79.10%) followed by BP response to sustained hand grip (63.16%) followed by Heart rate response to Valsalva (61.19%).

Heart rate response to deep breathing was the most specific test (93.94%) followed by Heart response to Valsalva (87.88%) and BP response to standing (87.88%).

So for parasympathetic testing Heart rate response to deep breathing was the most sensitive test and for sympathetic testing BP response to sustained hand grip was the most sensitive test.

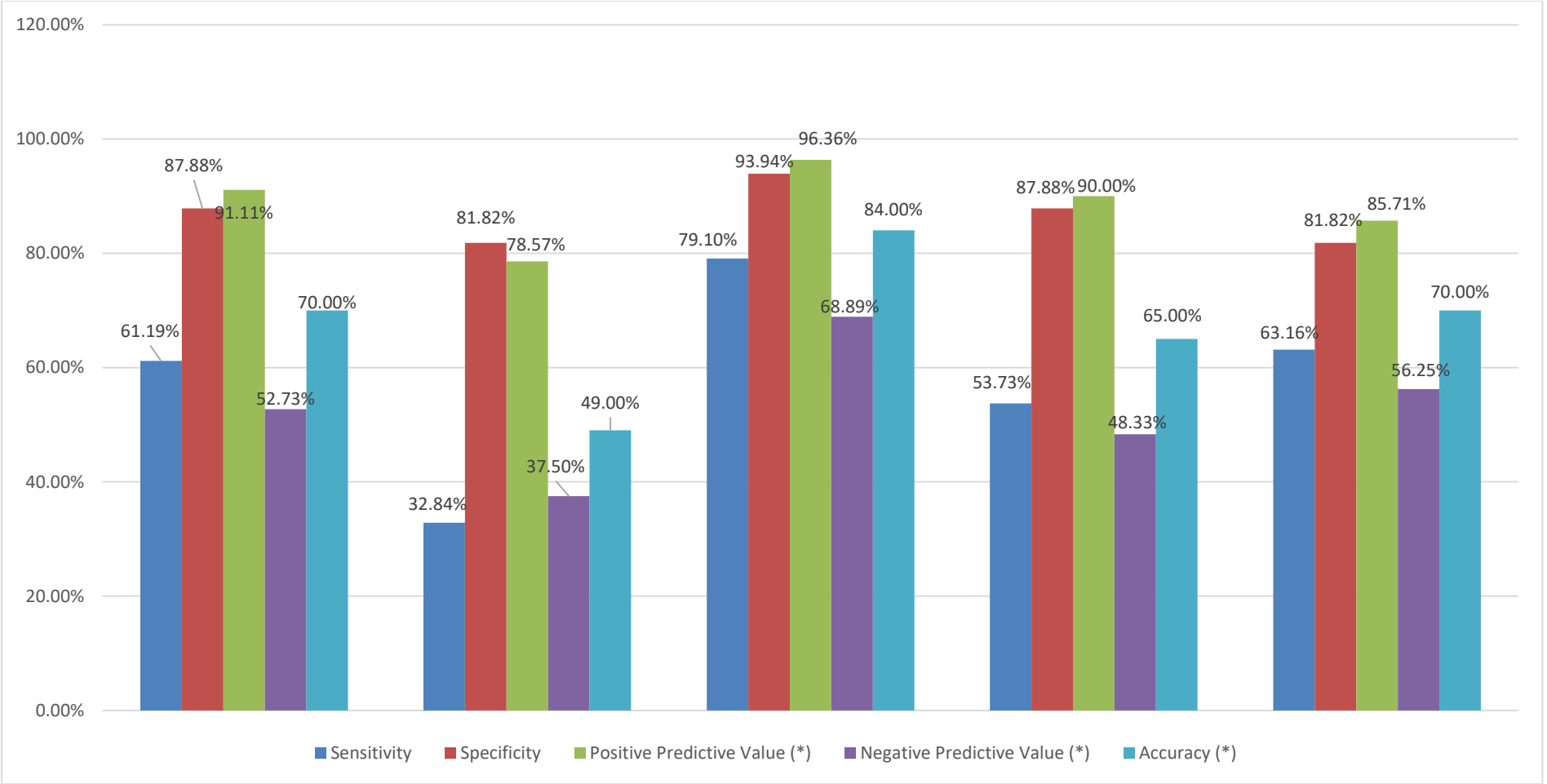

FIGURE 27: STATISTICAL ANALYSIS OF CAN TESTING

ROC CURVES

AGE

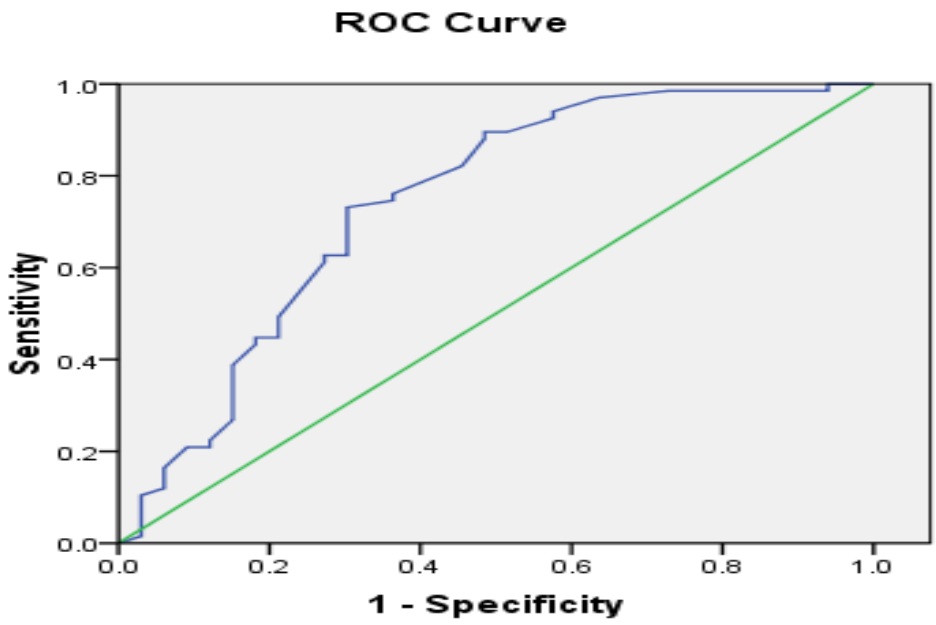

FIGURE 28: ROC CURVE SHOWING CORRELATION OF AGE WITH PRESENCE OF CAN

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Age	0.743	0.057	0.001	0.631	0.855

In the above ROC curve, area under is 0.743, so increasing age is a good predictor for CAN+. At a cut-off value of age ≥54.5 years CAN+ is highest.

DURATION OF DIABETES

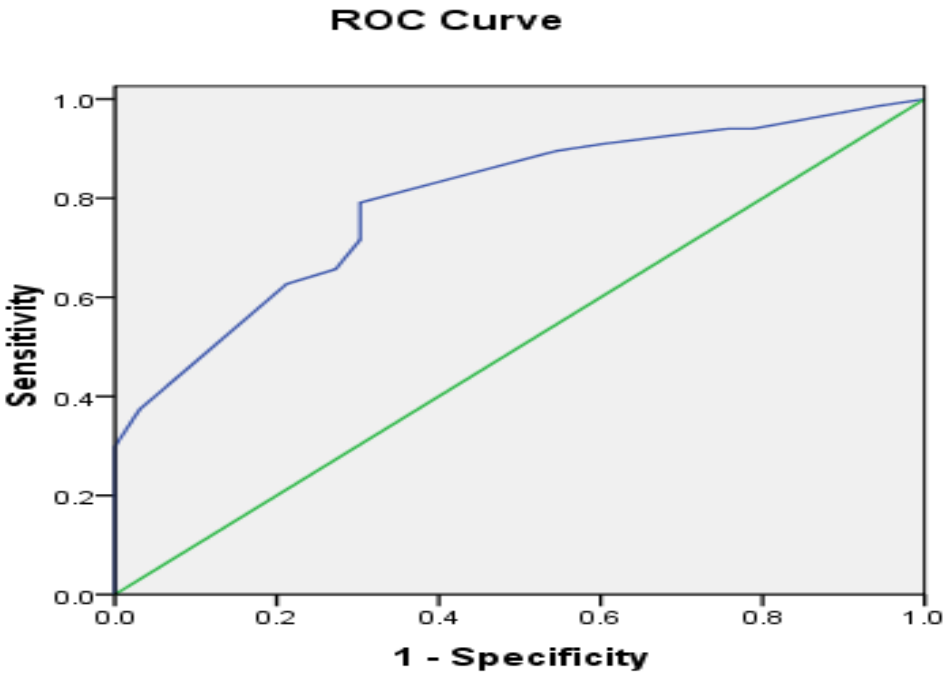

FIGURE 29: ROC CURVE SHOWING CORRELATION OF DURATION OF DIABETES WITH PRESENCE OF CAN

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Duration of Diabetes	0.795	0.045	0.001	0.706	0.883

In the above ROC curve, area under the curve is 0.795, so increasing duration of diabetes is good predictor of CAN+. At a cut-off value of duration of diabetes ≥5.5 years CAN+ is highest.

HBA1C

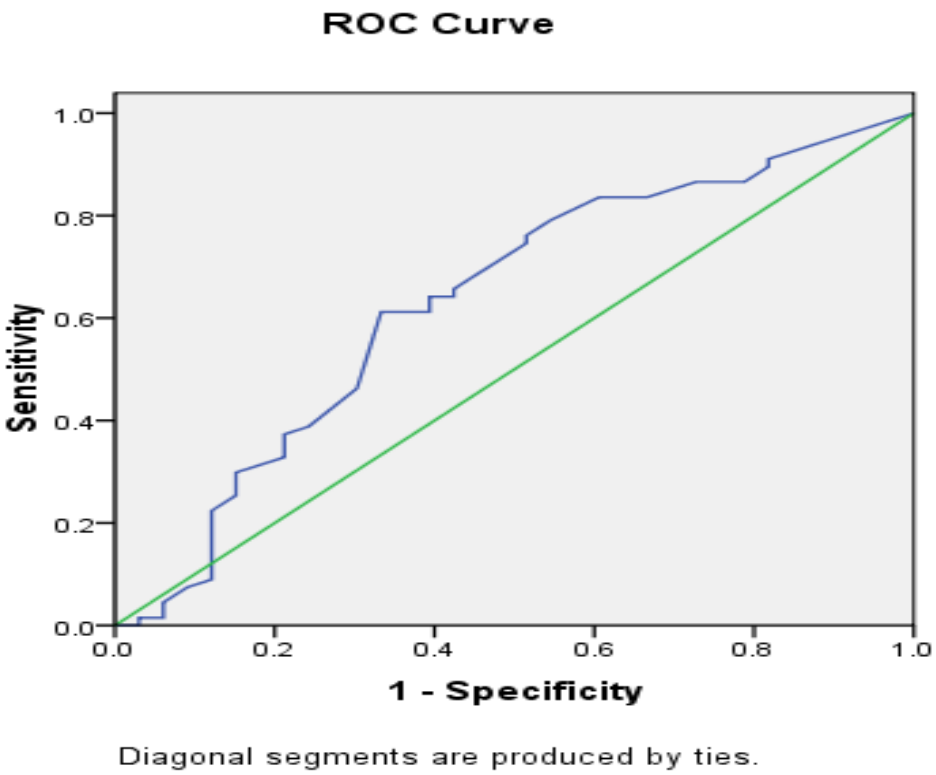

FIGURE 30: ROC CURVE SHOWING CORRELATION OF HbA1c WITH PRESENCE OF CAN

Area Under the Curve

Test Result Variable (s)	Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
HbA1C	0.633	0.062	0.031	0.512	0.753

In above ROC curve, area under the curve is 0.633, so HbA1C is not a good predictor of CAN+. At a cut off value of HbA1c ≥9 CAN positivity was highest.

DISCUSSION

The present cross sectional study conducted in a tertiary care hospital of North India was done on 100 Type 2 Diabetes mellitus patients to assess the frequency and pattern of cardiovascular autonomic dysfunction and also its association with micro-vascular complications of diabetes. Cardiovascular autonomic neuropathy is often an underdiagnosed complication of diabetes mellitus and is associated with increased mortality and morbidity.[4] CAN is associated with reduction in heart rate variability, resting tachycardia, orthostatic hypotension and sudden death syndrome; gastrointestinal manifestations that includes diabetic gastropathy, enteropathy and colonic hypomotility; urogenital manifestations that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction; sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis; abnormal pupillary function and hypoglycemic unawareness. [6] The observations, results and statistical data were compared with previous published literature.

DEMOGRAPHICS OF OUR STUDY GROUP

In our study of 100 patients, 59% were males and 41% were females with a Male: Female ratio of 1.43: 1. In a study done by Sumaswi et al [2] in South India there were 56% males and 44% females and in a study done in North East India by Bijaya et al [61] there were 57.5% males and 42.5% were females.

The mean age of our study subjects was 56.57±11.86 years with minimum age of 27 years and maximum age of 80 years. Maximum patients were found in age group 51-60 years with 33 patients (33%) followed by 61-70 years with 27 patients (27%). Minimum patients were found to have age less than 40 years that is 6(6%). It was similar to study done by Sumaswi et al [2] where mean age of subjects was 55.85±10.22 years. In a study done by Bhuyan et al [4] mean age was 53.3±10.37 years.

The mean duration of diabetes in our study population was 8.83±5.55 years with minimum duration of 1 year and maximum duration of 25 years. It was noticed that maximum patients that is 52 patients (52%) were having duration of diabetes of 5 to 10 years, 26 patients (26%) had duration of diabetes > 10 years and 22 patients (22%) had duration of diabetes of 1 to 5 years. Our study population was similar to study done by Bhuyan et all [4] where mean duration of diabetes was found to be 9.03±6.4 years. In the study done by Bijaya et al [61] 37.5% cases had diabetes with duration 0 to 5 years followed by 37.5% with duration >10 years and 25% with duration 6 to10 years. In a study done by Mathur et al [34] the maximum population had diabetes < 5 years that is 46% and in the study done by Brijadar et al [15] 62% subjects had diabetes of 0-2 years.

Regarding HbA1c, maximum patients in our study i.e 67 (67%) had HbA1c of 7.5-10 followed by 17 diabetics with HbA1c of 5-7.5 and 16 diabetics with HbA1c >10. The mean HbA1c observed in our study population was 8.95±1.39. In the study done Bijaya et al [61] out of 40 diabetic subjects, 10 had HbA1c of 6-7, 20 had HbA1c of 7-8 and 10 had HbA1c >8. Contrary to our study, in a study done by Bhuyan et al [4] mean HbA1c was higher that is 10.9. In a case control study done in 2006 in AIIMS, New Delhi by Jyotsna et al [65] on 205 subjects, mean HbA1c was 7.7±1.7 which was a better glycemic control than our subject population.

In our study population, maximum patients (50%) had complaints of tingling, burning, numbness, sharp stabbing pain and loss of sensation. 16 patients (16%) reported facial puffiness or pedal edema. 10 patients (10%) had visual complaints and 9 patients (9%) had complaints of dyspnea on exertion. 11 (18.6%) out of 59 males complained of erectile dysfunction. Erectile dysfunction was reported by 17.1% of study group studied by Bhuyan et al [4] and by 20% of subjects studied by Bijaya et al [61] which are quite similar results to our study.

CARDIAC AUTONOMIC NEUROPATHY TESTING

In our study, tests for assessment of cardiovascular autonomic neuropathy were done which consisted of 3 parasympathetic tests and 2 sympathetic tests. Results were interpreted as per Ewing's Criteria. Out of 100 subjects, we found presence of cardiac autonomic neuropathy in 67 patients (67%). The results were similar to study done in South India by Sumaswi et al [2] who reported CAN in 34 out of 50 subjects studied with prevalence of 68%. In the study done in East India by Bhuyan et al [4] 70 out of 100 subjects had CAN testing positive with prevalence of 70%. The study done by Ewing et al [35] reported 61% prevalence of CAN in 543 diabetic subjects which is lower than our study. Contrary to our study, study done by Sukla et al [1] on 126 subjects found CAN prevalence of 53.2%. Lower prevalence than our study were also reported by Brijadar et al [15], Mathur et al [34], Basu et al [36] and Bijaya et al[61] that is 58%, 58%,54% and 57.5% respectively. The reason for higher prevalence of CAN in our setup may be because people take medical attention late in the natural course of disease due to their ignorance about the disease.

The results were interpreted as per the Ewing's criteria as early, definite, severe and atypical CAN. Out of 67 patients (67%) with CAN positive, 22(22%) had early CAN, 9(9%) had definite CAN, 18(18%) had severe CAN and 18(18%) had atypical CAN.

TABLE 36: COMPARISON OF CAN TESTING RESULTS (BY EWING'S CRITERIA) OF OUR STUDY WITH OTHER STUDIES

CAN	Our study	Ewing et al [35]	Sumaswi et al [2]	Mathur et al [34]	Bhuyan et al [4]
EARLY	22%	15%	14%	20%	25%
DEFINITE	9%	18%	8%	30%	24%
SEVERE	18%	22%	14%	4%	21%
ATYPICAL	18%	6%	32%	4%	-
TOTAL	67%	61%	68%	58%	70%

So, early CAN in our study was similar to studies done by Mathur et al [34] and Bhuyan et al [4] while Sumaswi et al [2] and Ewing et al [35] had lower rate of early CAN. Mathur et al [34] and Bhuyan et al [4] had higher rate of definite CAN than our study. Severe CAN was similar to Ewing et al [35], Sumaswi et al [2] and Bhuyan et al [4] while Mathur et al [34] reported very low rate of severe CAN.

INDIVIDUAL ANALYSIS OF CAN TESTS

The abnormal response was found to be highest in heart rate response to deep breathing seen in 35 patients (35%) followed by heart rate response to valsalva maneuver seen in 29 patients (29%), heart rate response to standing seen in 11 patients (11%), BP response to sustained hand grip seen in 10 patients (10%) and least abnormal response with BP response to standing seen in 9 patients (9%). The results were similar as observed by Sumaswi et al [4] who reported heart rate response to deep breathing as the most frequent abnormal response seen in 36% patients followed by heart rate response to valsalva seen in 26% patients and followed by heart rate response to standing seen in 12% patients. Mathur et al [34] reported heart response to deep breathing as most frequent abnormal response seen in 48%

patients followed by heart rate response to valsalva seen in 34% patients and then followed by heart rate response to standing seen in 24% cases. In a study done by Ewing et al [35] on 543 diabetics most frequent abnormal response was heart rate response to deep breathing seen in 40% subjects similar to our study. However, the second most frequent abnormal test was heart rate response to standing seen in about 36% subjects followed by heart rate response to valsalva seen in 24% subjects. Bhuyan et al [4] also reported the heart rate response to deep breathing as most frequent abnormal response seen in 56% cases followed by heart rate response to standing seen in 42% cases and then followed by abnormal valsalva response in 32% cases. Contrary to our results, Brijadar et al [15] and Bijaya et al [61] reported heart rate response to standing as most frequent abnormal test seen in 38% and 27.5% of subjects. In all previous studies sympathetic tests were reported as being least frequent abnormal CAN test as compared to parasympathetic tests. This may be explained by fact that parasympathetic involvement precedes the sympathetic involvement.

In our study, parasympathetic testing was found to be positive in 59 patients (59%), sympathetic tests were positive in 37 patients (37%) and combined parasympathetic and sympathetic testing were positive in 29 patients (29%). Out of 100 patients 30 patients (30%) had parasympathetic tests positive alone and 8 patients (8%) had sympathetic tests positive alone. Studies done by Ramavat et al [64] reported that 39.1% had parasympathetic testing positive, 27% had sympathetic testing positive and 17.9% had combined parasympathetic and sympathetic testing positive. 17.9% had parasympathetic test positive alone and 6.5% had sympathetic tests positive alone. Compared to this study the results obtained in our study were higher. Sumaswi et al [2] reported parasympathetic dysfunction in 60%, sympathetic dysfunction in 48% subjects and combined parasympathetic + sympathetic in 40% subjects. 20% had parasympathetic dysfunction alone compared to 8% who had sympathetic dysfunction alone.

Sympathetic testing results were higher as compared to our study while parasympathetic testing results were almost the same as compared to our study. In a study done by Basu et al [36] 52% reported parasympathetic tests positive and 20% reported sympathetic tests positive. Our study had parasympathetic testing positivity quite similar to above study but sympathetic testing positivity rate was higher. Studies done by Brijadar et al [15] reported that parasympathetic involvement was seen in 48% with combined parasympathetic and sympathetic involvement in 10% cases with no case of isolated sympathetic involvement. Ewing et at [35] reported parasympathetic dysfunction in 55.73% and sympathetic dysfunction in 26.33% subjects. Jyotsna et al [65] showed sympathetic involvement of 51.9% which was greater than parasympathetic involvement of 44.2% which was contrary to our and all studies mentioned above. As per the available literature, it is not very clear why parasympathetic involvement is greater than sympathetic involvement in CAN. One of theories is that damage to parasympathetic fibres precedes sympathetic fibres. Another theory is that parasympathetic testing is more sensitive compared to sympathetic testing.

In our study heart rate response to deep breathing was the most sensitive test followed by BP response to sustained hand grip and then heart rate response to valsalva. Heart rate response to deep breathing was the most specific test followed by heart response to valsalva and BP response to standing. So, for parasympathetic testing heart rate response to deep breathing was the most sensitive test and for sympathetic testing BP response to sustained hand grip was the most sensitive test.

Out of all 5 tests done, heart rate response to deep breathing is the most accurate test with highest sensitivity of 79.10%, specificity of 93.94%, positive predictive value of 96.36%, and negative predictive value of 68.89% and accuracy of 84%.

RISK FACTORS ASSOCIATED WITH CAN

In our study, mean age in CAN+ group was much higher compared to mean age in CAN- group (59.9±10 years versus 49.82±12.61 years). It was observed that at an age of >50 years presence of CAN was 82.1% as compared to age <50 years with presence of CAN in 17.9%. Thus age had statistically significant correlation with presence of CAN with p value of 0.0001. On plotting ROC curve, area under the curve was 0.743, so increasing age was found to be a good predictor of CAN. At a cut off value of age ≥54.5 years CAN positivity rate was highest. These results were similar to study done by Bhuyan et al [4] where mean age of CAN+ group was 55.6±10.3 years which was higher compared to CAN- group with mean age of 47.93±8.51 years and they found that people who are older are at a greater risk of CAN . Similarly in a study done by Jyotsna et al [65] at AIIMS, New Delhi mean age was higher in CAN+ group as compared to CAN- group and correlation of age with presence of CAN was statistically significant. Bijaya et al [61] observed that there were more CAN+ patients in age group 61-70 years i.e 17.5% compared with age group 21-30 years i.e 2.5%. So he concluded increasing age had significant correlation with CAN.

There was no statistical correlation between gender and presence of CAN. Similar results were shown by study done by Bhuyan et al [4] and Bijaya et al [61].

Mean duration of diabetes in CAN+ was 10.60±5.62 years which was higher than CAN- group which had mean duration of 5.23±3.18 years. With duration of diabetes <5 years, 7 out of 22 subjects were positive for CAN, with duration 5-10 years, 39 out of 59 subjects were positive for CAN and with duration >10 years, 25 out of 26 subjects were positive for CAN. Correlation of CAN with duration of diabetes was statistically significant with p value of 0.0001. When ROC curve for duration of

diabetes was plotted, area under the curve was 0.795, so increasing duration of diabetes is a good predictor of CAN positivity. At a cut off value of duration of diabetes ≥5.5 years in our study CAN positivity rate was the highest. Bijaya et al [61] concluded that when duration of diabetes was greater than 10 years presence of CAN was 25% and in newly detected diabetics it was 7.5%. They also found a significant correlation between CAN and duration of diabetes. Bhuyan et al [4] also found a statistical significance between presence of CAN and duration of diabetes with p value<0.0001. Similarly, Mathur et al [34] found a significant correlation between CAN and duration of diabetes with incidence rising from 21.05% to 57.89% with duration increasing from 0-5 years to 5-10 years.

We could not establish any statistical correlation between presence of co-morbidities like hypertension and hypothyroidism and its effect on presence of CAN. Other co-morbidities like CAD and CRF were in exclusion criteria of our study as they affect CAN testing results.

In CAN+ group systolic BP was higher (means SBP-121.19 versus 116.36) compared to CAN- group and this was statistically significant. Diastolic BP was higher is CAN+ group (mean DBP-78.21 versus 75.76) and correlation was statistically significant. In the study done by Bhuyan et al [4] similar findings were reported with SBP and DBP being higher in CAN+ group but this correlation was not found to be statistically significant in their study. Resting heart rate was nearly equal in both groups and thus not found to be statistically significant. Although resting tachycardia was found in 11 patients with CAN+ and 6 patients with CAN-. Contrary to our study, Bhuyan et al [4] observed that resting heart rate was higher in CAN+ group compared to CAN- group with correlation being statistically significant.

Serum creatinine was higher in CAN+ group compared to CAN- group [mean creatinine-0.82 versus 0.67] and its correlation with presence of CAN was statistically significant respectively. It is well known that parasympathetic dysfunction precedes sympathetic dysfunction. As

renal glomeruli are heavily innervated by sympathetic fibres resulting in sympathetic over-activity after parasympathetic dysfunction, renal homeostasis is affected causing imbalance of blood flow causing progression to renal dysfunction. Bhuyan et al [4] also found statistical correlation of serum creatinine with presence of CAN as serum creatinine was higher in CAN+ group compared to CAN- group. Although dyslipidemia (increased LDL and increased TG's) are among the several risk factors in diabetics but studies have failed to prove the association between dyslipidemia and CAN. Dyslipidemia had no statistical correlation with presence of CAN in our study. Similar results were shown by study done by Bhuyan et al [4] who showed no correlation between lipid profile and CAN.

In our study, mean HbA1c was higher in CAN+ population than in CAN- population (9.07±1.21 versus 8.71±1.68). We found that out of 16 patients with HbA1c of 5-7.5, 9 were positive for CAN; out of 67 patients with HbA1c of 7.5-10, 45 were positive for CAN and out of 17 patients with HbA1c >10, 13 were positive for CAN. So, it was observed that with increasing HbA1c, presence of CAN+ also increased although we could not establish statistical significant correlation for the same. On plotting ROC curve of HbA1c, area under the curve was 0.633 so rising HbA1c is not a good predictor of CAN. It was however noted that at cut off value of HbA1c ≥9 CAN positivity was higher. HbA1c provides an idea about short term glycemic control and does not tell us about the glycemic status in last few years which is responsible for long term complications of diabetes. Similar to our study Bijaya et al [61] concluded that incidence of CAN was 7.5% at HbA1c < 7 which increased to 30% at HbA1c >8. Bhuyan et al [4] could not establish a statistical correlation between HbA1c and presence of CAN. Basu et al [36] observed that raised HbA1c was found in 20 out of 27 patients with CAN and 18 out of 23 patients without CAN in a study population of 50 diabetic subjects. He concluded that poor short term control had no correlation with prevalence of CAN. Similarly in a study done in AIIMS by Jyotsna et al [65], it was observed

that HbA1c was higher in CAN+ population as compared to CAN- population (8.1±2.2 versus 7.2±1.6) but no statistical correlation was found.

ASSOCIATION OF CAN WITH COMPLICATIONS OF DIABETES

In our study, overall incidence of erectile dysfunction was 18.6%. When presence of ED was compared in CAN+ versus CAN- group it was observed that ED was higher in CAN+ group compared to CAN- group (25.6% versus 5%). Further note was made that out of 11 males with erectile dysfunction, 5(45.45%) had severe CAN, 3 (27.27%) had definite CAN, 1 (9.09%) had early CAN, 1 (9.09%) had atypical CAN and 1 (9.09%) was normal. So severe CAN was more commonly seen in patients with ED. However we could not find any statistical correlation between ED and presence of CAN probably due to the smaller sample size of our male population. Thus males with ED should be screened for CAN to prevent the potential complications of CAN.

In our study group, 33 patients (33%) were found to have diabetic neuropathy. Diabetic neuropathy was present in 27 patients (40.3%) out of 67 patients who had CAN+ as compared to 6 patients (18.2%) out of 33 patients who had CAN-. So diabetic neuropathy was more common in patients with CAN and this relationship was statistically significant with p value of 0.0269. In a study done Vinik et al [19] in Toronto, Canada in 2009, diabetic neuropathy was present in 50% of his study population which is higher than our study. Bhuyan et al [4] did a study on 100 diabetic subjects out of which 70 subjects had CAN+ and all had diabetic neuropathy and p value was reported as <0.0001. In a study done by Brijadar et al [15] on 100 diabetic subjects 58 subjects had diabetic neuropathy out of which 42 subjects were CAN+. Contrary to above findings Kudrimoti et al [66] did not find any statistical correlation of CAN with diabetic neuropathy.

In our study, diabetics with CRF were excluded as CRF can affect the results of CAN testing. So we studied the association of albuminuria with

CAN. On comparing patients with albuminuria with CAN we established a statistical significant correlation between presence of CAN and albuminuria with p value of 0.032. In our study, urine albuminuria was seen in 49 patients (73.1%) out of 67 patients who had CAN+ as compared to 17 patients (51.5%) out of 33 patients who had CAN-. In a study done by Bhuyan et al [4] on 100 diabetic subjects, 70 had CAN+ and 64 out of them had diabetic nephropathy and p value reported was <0.0001. Basu et al [36] also found a statistical significant relation between micro-albuminuria and CAN with a p value of <0.005. Contrary to our study, Brijadar et al [15] and Kudrimoti et al [66] could not establish a statistical significant correlation between diabetic nephropathy and CAN.

Due to COVID-19 pandemic 40 patients in our study had their fundus examination done. 16 (40%) out of 40 patients showed presence of diabetic retinopathy on fundus examination. Diabetic retinopathy was present was seen in 12 patients (50%) out of 24 patients who had CAN+ as compared to 4 patients (25%) out of 16 patients who had CAN- . Diabetic retinopathy was more in CAN+ group as compared to CAN- group. However, we could not establish a statistical significant correlation between presence of CAN and diabetic retinopathy which was probably due to smaller number of patients who underwent fundus examination. Studies done by Gadkaria et al [63] found the prevalence of diabetic retinopathy as 21.7% which is lower than our study population. Similarly study done by Brijadar et al [15] could not establish a statistical significant correlation between CAN and diabetic retinopathy. In his study incidence of retinopathy was 56% which was higher than our study. Kudrimoti et al [66] reported incidence of retinopathy as 31.4% which is lower than our study and no statistical significance was found between CAN and diabetic retinopathy. Contrary to our study, Bhuyan et al [4] found that 64 out of 70 patients with CAN+ had retinopathy and p value was found as <0.0001. Basu et al [36] also found statistical

significant correlation between CAN and retinopathy with p value < 0.005.

On a final note, presence of CAN in diabetics is associated with increased mortality and morbidity. Paucity of associated symptoms leads to delay in detection of CAN. Number of non-invasive tests have been developed for diagnosis of CAN which are sensitive but are time consuming. Identifying CAN in its early phase by simple bed side tests can help to delay its progression and hence prevent the complications of CAN. CAN has direct correlation with duration of diabetes and increasing age. HbA1c is an index of short term glycemic control and has no correlation with chronic process like CAN. Chronic complications of diabetes like neuropathy and nephropathy resulting from long standing poor glycemic status have direct correlation with presence of CAN.

LIMITATIONS

- Single centered study.
- Long term follow up of the study population was not done.

SUMMARY AND CONCLUSION

1. The presence of CAN in 100 Type 2 diabetes mellitus patients was studied and classified according to Ewing's criteria.
2. Male preponderance was seen in our study with male: female ratio of 1.43:1.
3. Maximum patients in our study were in age group 51-60 years with the mean age of patients being 56.57±11.86 years.
4. Maximum patients had duration of diabetes 5-10 years with the mean duration of diabetes of study population being 8.83±5.55 years.
5. Maximum patients had HbA1c of 7.5-10 with mean HbA1c in our study population being 8.95±1.39.
6. The prevalence of CAN was found in 67 out of the 100 patients (67%) studied.
7. Maximum patients studied i.e 22 (22%) had early CAN, 9 patients (9%) had definite CAN, 18 patients (18%) had severe CAN and 18 patients (18%) had atypical CAN.
8. Heart rate response to deep breathing was most frequent abnormal test seen in 35 patients (35%) followed by heart rate response to valsalva manoeuvre seen in 29 patients (29%), heart rate response to standing seen in 11 patients (11%), BP response to sustained hand grip seen in 10 patients (10%) and least abnormal response was seen in BP response to standing in 9 patients (9%).
9. For Parasympathetic testing, heart rate response to deep breathing was most sensitive test and for sympathetic testing BP response to sustained hand grip was most sensitive test.
10. Parasympathetic testing was positive in 59 patients (59%) and sympathetic testing was positive in 37 patients (37%). Combined parasympathetic and sympathetic testing was positive in 29 patients (29%). Out of 100 patients 30 patients

(30%) had parasympathetic tests positive alone and 8 patients (8%) had sympathetic tests positive alone.

11. Increasing age, duration of diabetes and higher serum creatinine had statistical significant correlation with presence of CAN.
12. Gender, dyslipidemia, higher HbA1c and presence of co-existing morbidities (hypertension and hypothyroidism) had no correlation with presence of CAN.
13. Erectile dysfunction (ED) was present in 11 out of 59 males (18.6%) and was found to be more common in patients with CAN. Diabetic retinopathy was found to be higher in CAN+ group as compared to CAN- group but this correlation was not statistically significant.
14. Diabetic neuropathy and albuminuria were found to be higher in CAN+ group as compared to CAN- group and correlation with presence of CAN was statistically significant.

CONCLUSION

Cardiac autonomic neuropathy is an underdiagnosed complication of diabetes and carries high mortality and morbidity. 67% of our study subjects had cardiac autonomic neuropathy which is very significant. CAN positivity was associated with increasing age, greater duration of diabetes, diabetic neuropathy and albuminuria. HbA1c, gender and dyslipidemia had no effect on presence of CAN. Erectle dysfunction and diabetic retinopathy were higher in patients of CAN. So, CAN testing using simple bed side tests in patients of diabetes can help in early identification of CAN. Such CAN patients should be advised about tight glycemic control, lifestyle modifications and symptomatic treatment of orthostatic hypotension to prevent further complications of CAN.

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						TREATMENT HISTORY		HISTORY OF PRESENT ILLNESS						PAST HISTORY		GPE							
Sr. No	Name	Age	Gender	MRD No	Duration of Diabetes	OHAS	INSULIN	1. Tingling/Burning Sensation/Numbness/Sharp Jabbing Pain/Loss of	2. Facial Puffiness, Pedal Edema	3. Visual Complaints	4. Chest Pain on Exertion	5. Dyspnea on Exertion	6. Erectile Dysfunction	HYPERTENSION	OTHERS	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	Pallor	Edema	Icterus	JVP
1	PK	44Y	F	924115	7Y	Y	N	Y	N	N	N	N	N	Y	N	80	120/70	16	AFEBRILE	N	N	N	N
2	AK	32Y	F	924145	2Y	N	N	N	N	N	N	N	N	N	N	84	110/70	12	AFEBRILE	N	N	N	N
3	PC	80Y	M	926195	2Y	N	N	N	N	Y	N	N	N	N	N	80	110/70	12	AFEBRILE	N	N	N	N
4	VB	65Y	F	925729	1Y	N	N	Y	N	Y	N	Y	N	Y	N	100	110/70	16	AFEBRILE	N	N	N	N
5	KS	69Y	F	929051	15Y	Y	N	Y	N	N	N	N	N	N	HYPOTHYROIDISM	84	110/70	16	AFEBRILE	N	N	N	N
6	AH	35Y	M	931140	1Y	N	N	Y	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
7	BS	64Y	M	621776	10Y	Y	N	Y	N	N	N	N	N	Y	N	80	130/70	16	AFEBRILE	N	N	N	N
8	P	52Y	F	369254	6Y	N	Y	N	N	N	N	N	N	Y	N	84	140/90	12	AFEBRILE	N	N	N	N
9	AL	59 Y	M	932241	2Y	Y	N	Y	N	N	N	N	Y	N	OLD TB	100	130/90	12	AFEBRILE	N	N	N	N
10	SM	35Y	F	624956	3Y	Y	N	Y	N	N	N	N	N	Y	HYPOTHYROIDISM	80	110/70	16	AFEBRILE	N	N	N	N
11	RK	58Y	M	934668	13Y	Y	N	Y	N	N	N	N	N	N	N	100	120/80	16	AFEBRILE	N	N	N	N
12	GK	70Y	F	874153	15Y	N	Y	N	N	N	N	N	N	Y	N	90	120/80	16	AFEBRILE	N	N	N	N
13	JS	52Y	M	937388	7Y	N	N	N	N	N	N	N	N	N	N	80	110/70	16	AFEBRILE	N	N	N	N
14	HK	59Y	F	937077	10Y	Y	N	Y	N	N	N	N	N	N	N	80	110/70	16	AFEBRILE	N	N	N	N
15	KK	66Y	F	933916	5Y	Y	N	Y	Y	N	N	N	N	Y	N	80	110/70	12	AFEBRILE	N	N	N	N
16	AS	78Y	M	930797	6Y	Y	N	N	N	N	N	N	N	N	N	80	140/80	16	AFEBRILE	N	N	N	N
17	BS	42Y	M	938476	2.5Y	N	Y	Y	N	N	N	N	N	N	N	110	120/70	16	AFEBRILE	N	N	N	N
18	GA	57Y	M	691352	10Y	Y	N	N	N	N	N	N	N	N	N	84	110/70	18	AFEBRILE	N	N	N	N
19	GK	55Y	F	937358	12Y	Y	N	N	N	N	N	N	N	N	N	110	120/80	16	AFEBRILE	N	N	N	N
20	RK	67Y	F	939048	20Y	N	Y	Y	N	N	N	N	N	N	N	94	130/80	16	AFEBRILE	N	N	N	N
21	AGV	50Y	M	936279	10Y	N	Y	N	N	N	N	N	N	N	N	84	120//80	16	AFEBRILE	N	N	N	N
22	S	55Y	F	939835	12Y	Y	N	Y	N	N	N	N	N	N	N	96	110/70	16	AFEBRILE	N	N	N	N
23	SS	78Y	M	940016	10Y	Y	N	N	N	N	N	N	Y	N	N	100	120/80	16	AFEBRILE	N	N	N	N
24	SR	42Y	F	948423	8Y	N	Y	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
25	DS	72Y	M	939640	10Y	Y	N	Y	N	N	N	N	N	Y	N	72	110/70	16	AFEBRILE	N	N	N	N
26	JK	58Y	F	951346	7Y	Y	N	Y	Y	Y	N	N	N	Y	N	100	120/80	12	AFEBRILE	N	N	N	N
27	C	55Y	F	952381	10Y	N	Y	Y	Y	N	N	N	N	Y	N	80	110/70	12	AFEBRILE	N	N	N	N
28	JS	59Y	M	604336	10Y	Y	N	Y	N	N	N	N	N	N	N	100	110/70	16	AFEBRILE	N	N	N	N
29	ML	62Y	M	947020	15Y	N	Y	Y	N	N	N	N	Y	N	N	90	110/70	16	AFEBRILE	N	N	N	N
30	AS	68Y	M	955183	10Y	Y	Y	Y	N	N	N	N	N	Y	N	80	110/70	12	AFEBRILE	N	N	N	N
31	SR	60Y	F	948236	20Y	N	N	N	Y	N	N	N	N	Y	N	80	110/70	16	AFEBRILE	N	N	N	N

		Systemic Examination				Investigations																	CARDIAC AUTONOMIC NEUROPATHY TESTING										INTERPRETATION OF THE RESULTS (According to Ewing's
								3 Serum Electrolytes				5. Lipid Profile				6. Urine Routine			7. Fundus			10. Other Investigations		PARASYMPATHETIC TESTING						SYMPHATHETIC TESTING				
																								1. HEART RATE		2. HEART RATE		3. HEART RATE		4. BP RESONSE TO		5. BP RESPONSE TO		
Sr. No	Name	CNS	CVS	Per Abdomen	Respiratory System	1. Hemoglobin	2. Serum Creatinine	Sodium	Potassium	Chloride	4. SGPT	LDL	HDL	Triglycerides	Cholesterol	Urine Albumin	Urine Glucose	Urine Microscopy	Examination	8. ECG	9. Echo 2D (If Done)	HBAIC	Any other	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	
1	PK	NAD	NAD	NAD	NAD	10.3	0.72	132	4.7	95	16	132	36	236	197	3+	3+	N	NORMAL	NSR	N/D	9.7	NO	1.15	B	1	A	25	N	10	N	20	N	EARLY
2	AK	NAD	NAD	NAD	NAD	12.7	0.47	142	3.82	101	69	103	34	130	150	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.1	NO	1.22	N	1.06	N	23	N	15	B	10	A	ATYPICAL
3	PC	NAD	NAD	NAD	NAD	10.4	0.78	129	3.9	95	12	N/D	N/D	N/D	N/D	N	N	N	NORMAL	NSR	N/D	7.4	UPPER GI-BARRETS ESOPHAGUS	1.33	N	1.06	N	12	B	10	N	20	N	NORMAL
4	VB	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	12.4	0.7	139	4.5	108	39	N/D	N/D	N/D	N/D	N	N	EPITHELIAL CI	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.25	N	1.2	N	8	A	20	B	20	N	EARLY
5	KS	NAD	NAD	NAD	NAD	10.1	1.2	138	4.7	108	14	90	23	206	142	N	N	N	N/D	NSR	N/D	11.2	NO	1.14	B	1.06	N	20	N	8	N	15	B	ATYPICAL
6	AH	NAD	NAD	NAD	NAD	12.8	0.68	135	4.35	96	74	N/D	N/D	N/D	N/D	N	1+	N	NORMAL	NSR	N/D	6.9	NO	1.25	N	1.18	N	25	N	8	N	20	N	NORMAL
7	BS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.2	0.83	137	4.6	98	38	N/D	N/D	N/D	N/D	N	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.3	NO	1	A	1.07	N	20	N	10	N	30	N	EARLY
8	P	NAD	NAD	RT HYPOCH(	NAD	10.1	0.86	140	3.83	104	29	111	22	144	196	3+	N	CALCIUM OX	N/D	T WAVE INVERSION V2 AND T WAVE FLATTENING V1	LVH AND NORMAL LVEF-60%	7.8	NO	1.14	B	1.03	B	20	N	5	N	20	N	EARLY
9	AL	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.3	0.92	133	4.42	87	23	92	55	114	183	N	N	N	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	11.1	NO	1	A	1.06	N	5	A	5	N	20	N	DEFINITE
10	SM	NAD	NAD	NAD	NAD	10.4	0.8	133	4.2	96	39	120	56	102	176	1+	N	N	NORMAL	NSR	N/D	7.7	NO	1.25	N	1.25	N	13	B	5	N	25	N	NORMAL
11	RK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.2	1.2	133	4.1	101	39	N/D	N/D	N/D	N/D	N	N	RBC-10-12	SEVERE NDPR	NSR	N/D	9.1	NO	1.06	A	1.06	N	10	A	15	B	15	B	SEVERE
12	GK	NAD	NAD	NAD	NAD	10.5	1.1	130	4.5	110	51	N/D	N/D	N/D	N/D	3+	N	N	N/D	NSR	N/D	7.1	NO	1.25	N	1.06	N	10	A	5	N	20	N	EARLY
13	JS	NAD	NAD	NAD	NAD	11	0.61	133	4.1	98	18	N/D	N/D	N/D	N/D	1+	N	N	NORMAL	NSR	N/D	10.5	NO	1.14	B	1.06	N	20	N	5	N	25	N	NORMAL
14	HK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	12.1	0.47	131	4.7	99	19	N/D	N/D	N/D	N/D	1+	N	N	N/D	NSR	N/D	8.4	NO	1.14	B	1.06	N	13	B	5	N	20	N	EARLY
15	KK	NAD	NAD	NAD	NAD	11.2	0.56	135	3.58	93	20	N/D	N/D	N/D	N/D	TRACES	2+	8-10 PUS	MILD NDPR	NSR	N/D	8.9	NO	1.25	N	1.03	B	25	N	10	N	20	N	NORMAL
16	AS	NAD	NAD	NAD	NAD	13.4	1.03	141	4.19	104	32	N/D	N/D	N/D	N/D	TRACES	N	4-6 PUS	N/D	NSR	MILD CONCENTRIC LVH EF-60%	6.9	NO	1.25	N	1	A	12	B	35	A	13	B	ATYPICAL
17	BS	NAD	NAD	NAD	NAD	11.2	0.59	141	3.9	98	19	N/D	N/D	N/D	N/D	N	3+	20 PUS	NORMAL	LAD	N/D	7.8	NO	1.14	B	1.06	N	20	N	5	N	20	N	NORMAL
18	GA	NAD	NAD	NAD	NAD	11.6	1.1	130	4.1	98	21	59	24	131	101	N	N	40-50 PUS	N/D	NSR	N/D	11.1	NO	1.3	N	1.06	N	20	N	15	B	13	B	ATYPICAL
19	GK	NAD	NAD	NAD	NAD	10.9	0.71	138	4.12	101	22	139	29	218	247	N	N	2-4 PUS 65-7(	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1	A	1.06	N	5	A	5	N	20	N	DEFINITE
20	RK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.2	1.04	139	4.2	98	19	N/D	N/D	N/D	N/D	N	1+	70 PUS	N/D	NSR	N/D	8.5	NO	1	A	1.02	B	5	A	15	B	5	A	SEVERE
21	AGV	NAD	NAD	NAD	NAD	10.2	0.7	131	4.7	98	9	N/D	N/D	N/D	N/D	2+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.1	NO	1.14	B	1.06	N	12	B	5	N	20	N	EARLY
22	S	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.4	0.73	135	3.67	102	27	N/D	N/D	N/D	N/D	1+	N	RBC-15-30	N/D	NSR	N/D	10.1	NO	1	A	1.08	N	8	A	15	B	12	B	SEVERE
23	SS	NAD	NAD	NAD	NAD	11.4	0.7	141	3.8	98	22	37	25	99	78	N	N	RBC-10-12	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.5	NO	1	A	1.03	B	5	A	15	B	14	B	SEVERE
24	SR	NAD	NAD	NAD	NAD	10.2	0.75	131	3.9	98	9	N/D	N/D	N/D	N/D	N	2+	N	NORMAL	LAD	N/D	9.3	NO	1.25	N	1.03	B	28	N	8	N	20	N	NORMAL
25	DS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.3	0.7	142	3.8	99	53	N/D	N/D	N/D	N/D	3+	2+	N	N/D	NSR	N/D	7.1	NO	1.14	B	1.06	N	20	N	5	N	25	N	NORMAL
26	JK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.2	1.1	136	4.5	98	19	111	62	177	310	3+	2+	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.4	NO	1.3	N	1.06	N	10	A	5	N	20	N	EARLY
27	C	NAD	NAD	NAD	NAD	10.5	1.2	130	4.7	111	52	N/D	N/D	N/D	N/D	2+	N	30 PUS CELLS	N/D	V1 V2 T WAVE INVERSION	N/D	9.2	NO	1.25	N	1	A	13	B	35	A	13	B	ATYPICAL
28	JS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.7	0.86	141	3.97	107	19	N/D	N/D	N/D	N/D	2+	N	40 PUS CELLS	MILD NDPR	LAD	N/D	14.6	NO	1.25	N	1.06	N	20	N	15	B	20	N	NORMAL
29	ML	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.7	1	131	3.85	96	11	N/D	N/D	N/D	N/D	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.3	NO	1	A	1.06	N	5	A	5	N	20	N	DEFINITE
30	AS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.8	0.59	133	3.89	100	21	68	42	82	115	N	3+	N	N/D	NSR	N/D	9.1	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
31	SR	NAD	NAD	NAD	NAD	12.5	0.73	132	4.04	99	23	105	32	215	276	2+	N	RBC-200/HPF	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.4	NO	1	A	1.06	N	5	A	15	B	13	B	SEVERE

								HISTORY OF PRESENT ILLNESS						PAST HISTORY		GPE							
						TREATMENT HISTORY		1. Tingling/Burning Sensation/Numbness/Sharp Jabbing Pain/Loss of	2. Facial Puffiness, Pedal Edema	3. Visual Complaints	4. Chest Pain on Exertion	5. Dyspnea on Exertion	6. Erectile Dysfunction										
Sr. No	Name	Age	Gender	MRD No	Duration of Diabetes	OHAS	INSULIN							HYPERTENSION	OTHERS	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	Pallor	Edema	Icterus	JVP
32	S	75Y	F	193902	20Y	Y	N	Y	N	N	N	Y	N	Y	N	100	120/80	20	AFEBRILE	N	N	N	N
33	D	41Y	M	591062	2Y	N	N	N	N	N	N	N	N	N	N	92	110/70	16	AFEBRILE	N	N	N	N
34	GS	70Y	M	968163	20Y	N	Y	Y	Y	N	N	N	N	N	N	80	120/80	16	AFEBRILE	N	N	N	N
35	RR	80Y	F	958956	8Y	N	N	N	N	N	N	N	N	Y	N	100	140/80	20	AFEBRILE	N	N	N	N
36	SK	52Y	M	35417	5Y	N	Y	N	N	N	N	N	Y	N	N	84	120/80	16	AFEBRILE	N	N	N	N
37	KD	63Y	F	92556	10Y	N	Y	Y	N	N	N	N	N	Y	N	80	110/80	16	AFEBRILE	N	N	N	N
38	GS	60Y	M	896486	15Y	Y	N	N	N	N	N	N	N	N	N	96	120/80	16	AFEBRILE	N	N	N	N
39	D	61Y	M	963026	8Y	Y	N	Y	N	N	N	N	N	N	N	100	120/80	12	AFEBRILE	N	N	N	N
40	RRS	58Y	M	962920	10Y	Y	N	Y	N	N	N	N	N	Y	N	84	140/80	16	AFEBRILE	N	N	N	N
41	MS	42Y	M	896403	3Y	Y	N	N	N	N	N	N	N	Y	N	100	120/80	16	AFEBRILE	N	N	N	N
42	KL	69Y	F	591160	15Y	Y	N	Y	N	N	N	N	N	Y	N	84	130/90	16	AFEBRILE	N	N	N	N
43	P	56Y	F	899996	5Y	Y	N	Y	N	Y	N	N	N	N	N	78	120/80	16	AFEBRILE	N	N	N	N
44	VP	65Y	M	964547	20Y	N	Y	Y	Y	Y	N	N	Y	N	N	80	110/70	16	AFEBRILE	N	N	N	N
45	JS	74Y	M	960594	20Y	Y	N	N	N	N	N	N	N	Y	N	92	130/80	16	AFEBRILE	N	N	N	N
46	SR	50Y	F	975656	3Y	Y	N	N	N	N	N	N	N	N	N	68	120/80	16	AFEBRILE	N	N	N	N
47	DS	47Y	M	978156	10Y	Y	N	N	N	N	N	N	N	N	N	96	110/70	20	AFEBRILE	N	N	N	N
48	VKK	58Y	M	981308	1Y	N	N	N	N	N	N	N	N	Y	N	100	120/80	16	AFEBRILE	N	N	N	N
49	RK	55Y	M	981479	10Y	Y	N	N	N	N	N	N	N	N	N	86	110/70	16	AFEBRILE	N	N	N	N
50	KB	59Y	F	981456	6Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
51	GS	52Y	M	983064	6Y	Y	N	Y	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
52	IS	47Y	M	984286	3Y	N	Y	N	N	N	N	N	N	Y	N	88	120/80	16	AFEBRILE	N	N	N	N
53	MS	63Y	M	984236	12Y	Y	N	Y	N	N	N	N	Y	Y	N	84	120/80	16	AFEBRILE	N	N	N	N
54	VS	66Y	M	984655	12Y	N	Y	N	N	N	N	N	N	Y	N	90	130/80	16	AFEBRILE	N	N	N	N
55	HW	55Y	F	983633	12Y	N	N	Y	N	N	N	N	N	N	N	86	120/80	16	AFEBRILE	N	N	N	N
56	R	48Y	F	984888	3Y	Y	N	N	N	N	N	N	N	N	N	80	120/80	16	AFEBRILE	N	N	N	N
57	SK	53Y	F	636133	7Y	Y	N	Y	N	N	N	N	N	Y	N	80	120/80	20	AFEBRILE	N	N	N	N
58	VK	66Y	M	983522	20Y	N	Y	Y	N	N	N	N	N	Y	N	100	130/80	16	AFEBRILE	N	N	N	N
59	HK	45Y	F	578121	5Y	Y	N	N	N	N	N	N	N	N	N	96	120/80	16	AFEBRILE	N	N	N	N

		Systemic Examination				Investigations																		CARDIAC AUTONOMIC NEUROPATHY TESTING										INTERPRETATION OF THE RESULTS (According to Ewing's
												5. Lipid Profile				6. Urine Routine						10. Other Investigations		PARASYMPATHETIC TESTING						SYMPATHETIC TESTING				
								3 Serum Electrolytes											7. Fundus					1. HEART RATE		2. HEART RATE		3. HEART RATE		4. BP RESONSE TO		5. BP RESPONSE TO		
Sr. No	Name	CNS	CVS	Per Abdomen	Respiratory System	1. Hemoglobin	2. Serum Creatinine	Sodium	Potassium	Chloride	4. SGPT	LDL	HDL	Triglycerides	Cholesterol	Urine Albumin	Urine Glucose	Urine Microscopy	Examination	8. ECG	9. Echo 2D (If Done)	HBAIC	Any other	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	
32	S	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	12.6	1.2	138	3.5	90	20	N/D	N/D	N/D	N/D	N	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.4	UPPER GI ENDOSCOPY-NORMAL	1	A	1.03	B	5	A	15	B	5	A	SEVERE
33	D	NAD	NAD	NAD	NAD	12.4	0.66	135	4.5	100	66	98	21	175	274	N	N	N	N/D	NSR	N/D	6.9	NO	1.14	B	1.06	N	20	N	5	N	20	N	NORMAL
34	GS	NAD	NAD	NAD	NAD	10.2	1.2	136	4.08	99	21	N/D	N/D	N/D	N/D	2+	N	N	SEVERE NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.8	NO	1.25	N	1	A	12	B	35	A	13	B	ATYPICAL
35	RR	NAD	NAD	NAD	NAD	12.7	0.47	144	3.78	106	23	68	32	124	170	N	N	N	N/D	NSR	MILD CONCENTRIC LVH EF-60%	7.1	NO	1.25	N	1.06	N	8	A	5	N	20	N	EARLY
36	SK	NAD	NAD	NAD	NAD	13	0.47	132	3.9	99	91	70	36	166	213	N	N	N	N/D	NSR	N/D	9.8	NO	1.25	N	1.06	N	20	N	15	B	20	N	NORMAL
37	KD	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.8	0.83	126	4.9	95	172	N/D	N/D	N/D	N/D	N	2+	N	N/D	NSR	N/D	7.2	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
38	GS	NAD	NAD	NAD	NAD	14.8	0.7	138	4.5	99	28	123	31	142	152	N	3+	N	N/D	NSR	N/D	9.4	NO	1	A	1.06	N	8	A	6	N	20	N	DEFINITE
39	D	NAD	NAD	NAD	NAD	10.9	0.41	142	3.8	99	9	N/D	N/D	N/D	N/D	N	N	N	N/D	NSR	N/D	11.1	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
40	RRS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.3	1	139	3.73	108	16	N/D	N/D	N/D	N/D	N	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.3	NO	1.15	B	1.06	N	13	B	5	N	20	N	EARLY
41	MS	NAD	NAD	NAD	NAD	12.1	0.43	131	3.9	102	72	134	56	180	172	1+	N	N	N/D	NSR	MILD CONCENTRIC LVH EF-60%	8.5	NO	1.25	N	1.03	B	20	N	5	N	20	N	NORMAL
42	KL	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.3	0.82	136	3.6	97	8	78	32	120	170	2+	1+	N	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.6	NO	1	A	1.06	N	5	A	5	N	20	N	DEFINITE
43	P	NAD	NAD	NAD	NAD	12.4	0.7	141	3.7	98	98	135	36	185	192	1+	N	N	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.1	NO	1.25	N	1.02	B	20	N	8	N	25	N	NORMAL
44	VP	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	14.6	0.8	131	3.9	102	62	84	58	170	248	N	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.1	NO	1	A	1.01	B	5	A	15	B	5	A	SEVERE
45	JS	NAD	NAD	NAD	NAD	10.5	1.01	138	3.88	98	11	144	46	178	221	3+	2+	N	MILD NDPR	NSR	MILD CONCENTRIC LVH EF-60%	9.9	NO	1.25	N	1	A	13	B	5	A	15	B	ATYPICAL
46	SR	NAD	NAD	NAD	NAD	10.1	1.02	136	3.8	99	18	72	42	118	156	1+	1+	1-2 PUS	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.1	NO	1.15	B	1.06	N	13	B	5	N	20	N	EARLY
47	DS	NAD	NAD	NAD	NAD	11.8	0.8	131	4.8	98	131	82	53	162	183	3+	N	80-85 RBC/HI	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.4	NO	1.25	N	1.06	N	5	A	5	N	25	N	EARLY
48	VKK	NAD	NAD	NAD	NAD	10.8	0.8	141	3.9	98	18	134	36	164	176	N	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.8	NO	1.25	N	1.03	B	20	N	5	N	20	N	NORMAL
49	RK	NAD	NAD	NAD	NAD	14.5	0.46	136	3.9	105	121	110	56	132	165	1+	N	RBC 2-4 PUS 2	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.25	N	1.06	N	20	N	15	B	15	B	ATYPICAL
50	KB	NAD	NAD	NAD	NAD	11.2	1.2	133	4.2	98	18	111	55	133	210	N	N	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.9	NO	1	A	1	A	20	N	15	B	13	B	SEVERE
51	GS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13	0.6	131	4.7	106	78	85	35	126	220	2+	1+	N	NORMAL	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.8	NO	1.06	A	1.06	N	20	N	5	N	20	N	EARLY
52	IS	NAD	NAD	NAD	NAD	12.8	0.6	133	3.6	101	97	135	35	168	235	N	N	N	N/D	NSR	MILD CONCENTRIC LVH EF-60%	8.2	NO	1.25	N	1.03	B	20	N	5	N	20	N	NORMAL
53	MS	NAD	NAD	NAD	NAD	11.5	0.92	135	4.8	101	133	155	35	165	220	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.5	NO	1.15	B	1.06	N	14	B	5	N	20	N	EARLY
54	VS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	14	0.92	133	4.5	98	655	155	62	166	198	N	N	N	N/D	LAD	MILD CONCENTRIC LVH EF-60%	9.3	NO	1.25	N	1	A	13	B	35	A	13	B	ATYPICAL
55	HW	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.1	0.96	133	4.7	101	53	115	62	170	212	1+	N	15-20 PUS	N/D	V1 V2 T WAVE INVERSION	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.1	NO	1	A	1.03	B	5	A	15	B	5	A	SEVERE
56	R	NAD	NAD	NAD	NAD	11.1	0.6	141	3.8	92	550	23	19	66	159	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.4	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
57	SK	NAD	NAD	NAD	NAD	11.5	0.53	138	4.2	98	65	34	32	144	201	1+	1+	N	N/D	NSR	N/D	7.2	NO	1	A	1.04	N	10	A	5	N	20	N	DEFINITE
58	VK	NAD	NAD	NAD	NAD	12.2	0.52	133	4.2	101	19	31	28	100	120	1+	N	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1	A	1.06	N	8	A	15	B	13	B	SEVERE
59	HK	NAD	NAD	NAD	NAD	11.2	0.9	141	3.9	105	19	68	62	124	131	1+	N	N	N/D	NSR	N/D	8.4	NO	1.25	N	1.06	N	20	N	5	N	13	B	NORMAL

								HISTORY OF PRESENT ILLNESS						PAST HISTORY		GPE							
						TREATMENT HISTORY		1. Tingling/Burning Sensation/Numbness/Sharp Jabbing Pain/Loss of	2. Facial Puffiness, Pedal Edema	3. Visual Complaints	4. Chest Pain on Exertion	5. Dyspnea on Exertion	6. Erectile Dysfunction										
Sr. No	Name	Age	Gender	MRD No	Duration of Diabetes	OHAS	INSULIN							HYPERTENSION	OTHERS	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	Pallor	Edema	Icterus	JVP
60	RK	52Y	M	790329	5Y	N	N	N	N	N	N	N	N	Y	N	80	120/80	16	AFEBRILE	N	N	N	N
61	PSD	52Y	M	9162	10Y	Y	N	Y	Y	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
62	RR	45Y	F	986522	5Y	Y	N	N	N	N	N	N	N	N	N	80	120/80	16	AFEBRILE	N	N	N	N
63	MD	40Y	M	994785	2Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
64	MS	69Y	M	337215	14Y	Y	N	Y	Y	Y	N	N	N	Y	N	96	120/80	16	AFEBRILE	N	N	N	N
65	SLK	69Y	M	996908	12Y	Y	N	N	N	N	N	N	N	N	N	80	120/80	20	AFEBRILE	N	N	N	N
66	GK	60Y	F	933549	18Y	Y	N	Y	N	N	N	N	N	N	N	96	120/80	16	AFEBRILE	N	N	N	N
67	GS	55Y	M	980199	7Y	N	N	N	N	N	N	N	N	N	N	90	130/80	16	AFEBRILE	N	N	N	N
68	PS	54Y	M	4259	5Y	Y	N	N	N	N	N	N	N	Y	N	96	130/80	16	AFEBRILE	N	N	N	N
69	PK	50Y	M	778714	2Y	N	N	N	N	N	N	N	N	N	N	100	130/80	16	AFEBRILE	N	N	N	N
70	ML	43Y	M	1003941	3Y	N	Y	Y	N	N	N	N	Y	N	N	80	120/80	16	AFEBRILE	N	N	N	N
71	GK	29Y	F	214687	5Y	N	Y	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
72	RBY	63Y	M	407289	10Y	Y	N	Y	N	N	N	N	Y	N	N	80	130/80	16	AFEBRILE	N	N	N	N
73	HL	40Y	F	1004418	5Y	Y	N	N	N	N	N	N	N	N	N	82	110/70	20	AFEBRILE	N	N	N	N
74	AJ	63Y	F	1003360	10Y	Y	N	Y	N	N	N	N	N	Y	N	100	120/80	16	AFEBRILE	N	B/L PEDAL	N	N
75	SS	79Y	M	952696	20Y	Y	N	Y	Y	Y	N	Y	Y	N	N	96	130/80	16	AFEBRILE	N	N	N	N
76	SG	39Y	M	1014346	4Y	Y	N	N	N	N	N	N	N	N	N	84	110/70	16	AFEBRILE	N	N	N	N
77	BKS	64Y	M	1010818	10Y	N	Y	Y	N	N	N	N	N	Y	N	72	130/80	16	AFEBRILE	N	N	N	N
78	VD	72Y	F	1013773	20Y	Y	N	Y	Y	Y	N	Y	N	Y	N	84	120/80	16	AFEBRILE	N	N	N	N
79	SD	78Y	F	6157	25Y	Y	N	Y	Y	Y	N	Y	N	Y	N	80	120/80	16	AFEBRILE	N	N	N	N
80	CS	50Y	M	1024732	5Y	N	N	Y	N	N	N	N	N	Y	N	84	120/80	16	AFEBRILE	N	N	N	N
81	KK	43Y	F	1026969	5Y	Y	N	N	N	N	N	N	N	Y	N	84	120/80	16	AFEBRILE	N	N	N	N
82	MS	27Y	M	1032184	3Y	N	Y	N	N	N	N	N	N	N	N	100	110/70	16	AFEBRILE	N	N	N	N

		Systemic Examination				Investigations																	CARDIAC AUTONOMIC NEUROPATHY TESTING										INTERPRETATION OF THE RESULTS (According to Ewing's
								3 Serum Electrolytes				5. Lipid Profile				6. Urine Routine							10. Other Investigations		PARASYMPATHETIC TESTING						SYMPATHETIC TESTING				
																							1. HEART RATE		2. HEART RATE		3. HEART RATE		4. BP RESONSE TO		5. BP RESPONSE TO		
Sr. No	Name	CNS	CVS	Per Abdomen	Respiratory System	1. Hemoglobin	2. Serum Creatinine	Sodium	Potassium	Chloride	4. SGPT	LDL	HDL	Triglycerides	Cholesterol	Urine Albumin	Urine Glucose	Urine Microscopy	7. Fundus Examination	8. ECG	9. Echo 2D (If Done)	HBAIC	Any other	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	
60	RK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.2	0.92	133	4.2	102	65	125	35	173	212	1+	N	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1.25	N	1.06	N	25	N	15	B	15	B	ATYPICAL
61	PSD	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.2	0.89	141	3.8	96	117	54	40	110	123	N	3+	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	6.9	NO	1.25	N	1.06	N	5	A	5	N	20	N	EARLY
62	RR	NAD	NAD	NAD	NAD	10.1	0.9	131	3.8	98	115	N/D	N/D	N/D	N/D	1+	1+	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.4	NO	1	A	1.06	N	6	A	5	N	20	N	DEFINITE
63	MD	NAD	NAD	NAD	NAD	14.2	0.9	141	3.9	96	65	N/D	N/D	N/D	N/D	1+	1+	N	N/D	NSR	N/D	8.1	NO	1.25	N	1.06	N	20	N	5	N	15	B	NORMAL
64	MS	NAD	NAD	NAD	NAD	10.1	1.2	131	4.9	106	115	62	35	160	185	1+	N	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.25	N	1.06	N	20	N	15	B	15	B	ATYPICAL
65	SLK	NAD	NAD	NAD	NAD	10.2	0.9	142	4.2	101	19	98	32	162	210	1+	N	PUS-FULL FIEI	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.9	NO	1.25	N	1.06	N	20	N	15	B	20	N	NORMAL
66	GK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.2	0.9	132	4.5	98	45	N/D	N/D	N/D	N/D	1+	N	N	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.8	NO	1	A	1.02	B	5	A	15	B	5	A	SEVERE
67	GS	NAD	NAD	NAD	NAD	10.2	0.9	133	4.8	102	15	N/D	N/D	N/D	N/D	2+	N	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.15	B	1.06	N	12	B	5	N	20	N	EARLY
68	PS	NAD	NAD	NAD	NAD	14.6	0.9	142	4.12	101	15	N/D	N/D	N/D	N/D	2+	N	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.1	NO	1.25	N	1.06	N	20	N	20	B	20	N	NORMAL
69	PK	NAD	NAD	NAD	NAD	14.2	0.9	132	4.1	102	16	80	62	162	234	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.2	NO	1.25	N	1	A	13	B	35	A	15	B	ATYPICAL
70	ML	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.1	0.9	133	4.2	98	65	40	33	144	159	1+	1+	10-12 PUS	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.8	NO	1	A	1.02	B	5	A	15	B	5	A	SEVERE
71	GK	NAD	NAD	NAD	NAD	11.1	0.23	140	3.9	101	17	35	28	140	160	N	N	N	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1.25	N	1.06	N	20	N	5	N	13	B	NORMAL
72	RBY	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	11.1	0.5	139	4.1	97	23	98	51	160	230	1+	1+	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1.25	N	1.06	N	20	N	15	B	15	B	ATYPICAL
73	HL	NAD	NAD	NAD	NAD	11.7	0.5	139	4.2	101	10	65	30	101	215	1+	1+	N	N/D	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.9	NO	1.25	N	1.06	N	20	N	5	N	14	B	NORMAL
74	AJ	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	12	0.5	140	4.1	98	15	102	35	165	199	3+	2+	6-10 PUS CEL	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.7	NO	1	A	1.03	B	5	A	15	B	5	A	SEVERE
75	SS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10	0.3	138	4.2	103	19	72	33	184	195	1+	N	10-15 PUS CE	NORMAL	LAD V1-V4 T WAVE FLATTENING	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.6	NO	1	A	1.06	N	5	A	15	B	13	B	SEVERE
76	SG	NAD	NAD	NAD	NAD	16	0.5	140	4.7	95	14	95	53	213	280	N	N	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1.25	N	1.06	N	20	N	5	N	14	B	NORMAL
77	BKS	NAD	NAD	NAD	NAD	10.4	0.53	136	4.5	101	16	85	29	123	179	1+	N	N	SEVERE NDPR	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.4	NO	1	A	1.06	N	5	A	5	N	25	N	DEFINITE
78	VD	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.1	0.75	130	4.7	96	17	102	19	176	211	2+	1+	16-20 PUS CE	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.1	NO	1.25	N	1.06	N	5	A	5	N	25	N	EARLY
79	SD	NAD	NAD	NAD	NAD	10.9	0.5	140	4.1	102	17	71	19	175	213	2+	1+	40-50 PUS CE	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.4	NO	1.15	B	1.06	N	13	B	5	N	20	N	EARLY
80	CS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.9	0.52	136	4.2	98	25	132	35	175	212	2+	1+	NO	N/D	NSR	MILD CONCENTRIC LVH EF-60%	11.9	NO	1.25	N	1	A	13	B	35	A	15	B	ATYPICAL
81	KK	NAD	NAD	NAD	NAD	13.1	0.92	130	4.1	95	24	131	55	174	212	1+	1+	NO	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.2	NO	1.15	B	1.06	N	13	B	5	N	20	N	EARLY
82	MS	NAD	NAD	NAD	NAD	13	0.82	140	3.8	102	45	65	23	155	212	N	N	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	13.01	NO	1.25	N	1.06	N	20	N	5	N	15	B	NORMAL

						TREATMENT HISTORY		HISTORY OF PRESENT ILLNESS						PAST HISTORY		GPE							
Sr. No	Name	Age	Gender	MRD No	Duration of Diabetes	OHAS	INSULIN	1. Tingling/Burning Sensation/Numbness/Sharp Jabbing Pain/Loss of	2. Facial Puffiness, Pedal Edema	3. Visual Complaints	4. Chest Pain on Exertion	5. Dyspnea on Exertion	6. Erectile Dysfunction	HYPERTENSION	OTHERS	Pulse Rate	Blood Pressure	Respiratory Rate	Temperature	Pallor	Edema	Icterus	JVP
83	SS	65Y	M	1018682	10Y	Y	N	N	N	N	N	Y	Y	N	N	82	120/80	16	AFEBRILE	N	N	N	N
84	HK	50Y	F	934980	10Y	N	Y	Y	Y	N	N	Y	N	N	N	88	110/70	16	AFEBRILE	N	N	N	N
85	KS	66Y	M	1094136	10Y	Y	N	Y	Y	N	N	N	N	Y	N	88	130/80	16	AFEBRILE	N	B/L PEDAL	N	N
86	MS	52Y	M	1050471	4Y	Y	N	Y	Y	N	N	N	N	N	N	80	130/80	16	AFEBRILE	N	N	N	N
87	VK	55Y	M	1067031	5Y	Y	N	N	N	N	N	Y	N	Y	N	90	120/80	16	AFEBRILE	N	N	N	N
88	SS	59Y	M	1067633	6Y	N	Y	N	Y	N	N	N	N	Y	N	84	110/70	16	AFEBRILE	N	N	N	N
89	VS	42Y	M	1073346	5Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	20	AFEBRILE	N	N	N	N
90	R	58Y	M	1072182	8Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	90	120/80	16	AFEBRILE	N	N	N	N
91	RK	43Y	M	1112819	2Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
92	CK	65Y	F	1023287	10Y	Y	N	Y	N	N	N	N	N	N	N	80	110/70	16	AFEBRILE	N	N	N	N
93	BS	64Y	M	1116086	14Y	N	Y	N	N	N	N	N	N	Y	N	84	130/90	16	AFEBRILE	N	N	N	N
94	RS	54Y	M	1117377	4Y	N	Y	Y	N	N	N	N	N	N	N	90	120/80	16	AFEBRILE	N	N	N	N
95	AK	40Y	F	1120093	2Y	N	Y	N	N	N	N	N	N	N	N	98	110/70	16	AFEBRILE	N	N	N	N
96	GK	54Y	F	1120790	10Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N
97	MD	70Y	F	1121816	15Y	Y	N	N	N	N	N	N	N	N	N	80	120/80	16	AFEBRILE	N	N	N	N
98	RS	43Y	F	1121935	5Y	N	N	Y	N	N	N	N	N	N	N	96	120/80	16	AFEBRILE	N	N	N	N
99	JS	64Y	M	1131414	10Y	Y	N	N	N	N	N	N	N	N	N	94	120/80	16	AFEBRILE	N	N	N	N
100	GS	49Y	M	1128344	5Y	Y	N	N	N	N	N	N	N	N	N	84	120/80	16	AFEBRILE	N	N	N	N

		Systemic Examination				Investigations																	CARDIAC AUTONOMIC NEUROPATHY TESTING												INTERPRETATION OF THE RESULTS (According to Ewing's
												5. Lipid Profile				6. Urine Routine							PARASYMPHATHETIC TESTING						SYMPHATHETIC TESTING					
								3 Serum Electrolytes											7. Fundus			10. Other Investigations		1. HEART RATE		2. HEART RATE		3. HEART RATE		4. BP RESONSE TO		5. BP RESPONSE TO		
Sr. No	Name	CNS	CVS	Per Abdomen	Respiratory System	1. Hemoglobin	2. Serum Creatinine	Sodium	Potassium	Chloride	4. SGPT	LDL	HDL	Triglycerides	Cholesterol	Urine Albumin	Urine Glucose	Urine Microscopy	Examination	8. ECG	9. Echo 2D (If Done)	HBAIC	Any other	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	RECORDED VALUE	INTERPRETATION	
83	SS	NAD	NAD	NAD	NAD	11.5	0.5	142	3.9	101	45	72	33	211	270	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1	A	1.06	N	5	A	5	N	20	N	DEFINITE
84	HK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.1	0.4	133	4.2	101	24	101	55	212	283	1+	1+	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.5	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
85	KS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	13.2	0.5	131	4.3	101	65	62	31	105	183	1+	N	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	13.2	NO	1	A	1.06	N	5	A	15	B	13	B	SEVERE
86	MS	NAD	NAD	NAD	NAD	10.1	0.52	140	3.8	103	101	115	32	172	212	1+	1+	4-6 PUS CELLS	NORMAL	LAD	NORMAL LV SYSTOLIC FUNCTION EF-60%	7.9	NO	1.25	N	1.06	N	20	N	8	N	20	N	NORMAL
87	VK	NAD	NAD	NAD	NAD	14.2	0.92	130	4.2	95	28	142	36	211	289	2+	1+	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.25	N	1.06	N	20	N	15	B	13	B	ATYPICAL
88	SS	NAD	NAD	NAD	NAD	10.1	0.98	139	3.5	106	53	116	31	201	250	2+	1+	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.3	N	1	A	14	B	35	A	15	B	ATYPICAL
89	VS	NAD	NAD	NAD	NAD	12.9	0.9	141	4.1	105	49	91	41	175	233	N	N	10-12 PUS CE	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.2	NO	1.25	N	1.06	N	5	A	5	N	20	N	EARLY
90	R	NAD	NAD	NAD	NAD	10.2	1.1	133	4.7	102	52	94	35	174	220	3+	2+	4-6 PUS CELLS	MILD NDPR	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.2	NO	1	A	1.03	B	10	A	15	B	5	A	SEVERE
91	RK	NAD	NAD	NAD	NAD	13.1	0.9	132	4.5	101	42	42	24	115	155	N	N	N	NORMAL	NSR	N/D	7.6	NO	1.25	N	1.06	N	20	N	5	N	20	N	NORMAL
92	CK	NAD	NAD	NAD	NAD	12.1	1.1	142	3.8	101	52	45	21	123	158	1+	N	40-50 PUS CE	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.2	NO	1	A	1.03	B	8	A	15	B	5	A	SEVERE
93	BS	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.9	0.52	141	3.8	105	52	101	24	181	230	1+	2+	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.1	NO	1.25	N	1	A	13	B	35	A	13	B	ATYPICAL
94	RS	NAD	NAD	NAD	NAD	10.1	1.05	133	4.5	101	53	101	24	153	177	2+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.1	NO	1.15	B	1.06	N	13	B	5	N	20	N	EARLY
95	AK	NAD	NAD	NAD	NAD	10.5	1.06	141	4.53	106	53	83	41	212	270	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.1	NO	1.3	N	1.08	N	20	N	5	N	25	N	NORMAL
96	GK	DIABETIC NEUROPATHY PRESENT	NAD	NAD	NAD	10.1	0.7	142	3.8	102	56	52	23	166	189	N	N	4-6 PUS CELLS	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.5	N	1.3	N	1.06	N	15	N	5	N	20	N	NORMAL
97	MD	NAD	NAD	NAD	NAD	12.4	0.5	133	4.5	105	53	148	66	156	222	2+	2+	N	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	10.5	N	1	A	1.06	N	5	A	15	B	13	B	SEVERE
98	RS	NAD	NAD	NAD	NAD	10.1	0.5	133	4.7	101	58	111	41	172	258	1+	N	40 PUS CELLS	NORMAL	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	8.7	N	1.25	N	1.06	N	20	N	5	N	25	N	NORMAL
99	JS	NAD	NAD	NAD	NAD	10.5	0.5	141	3.8	101	52	67	24	171	154	3+	N	N	N/D	NSR	MILD CONCENTRIC LVH EF-60%	9.8	N	1.25	N	1.06	N	5	A	5	N	20	N	EARLY
100	GS	NAD	NAD	NAD	NAD	10.1	0.86	131	4.5	97	20	N/D	N/D	N/D	N/D	1+	N	N	N/D	NSR	NORMAL LV SYSTOLIC FUNCTION EF-60%	9.5	N	1.25	N	1.06	N	20	N	15	B	13	B	ATYPICAL

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Date 20/4/2021

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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of **Dr. Ujjwal Mahajan**, a student of your college for **MD General Medicine** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Study of cardiovascular autonomic neuropathy in type 2 diabetes mellitus

Supervisor
Dr. Harmeet Pal Singh
Dhooria
Assoc. Prof.,
Dept. of Medicine,

Co-Supervisor
Dr. Dinesh Gupta
Prof. & Head,
Dept. of Medicine,
DMCH, Ludhiana.
Dr. Parminder Singh
Prof. & Head,
Dept. of Endocrinology,
DMCH. Ludhiana.

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. ***If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.***
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN

MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

NOVEMBER, 2019

DR. UJJWAL MAHAJAN

DEPARTMENT OF MEDICINE
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Study of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus
For the degree of	M.D. Medicine
Name of the candidate	Dr. Ujjwal Mahajan
Supervisor	Dr. Harmeet Pal Singh Dhooria Associate Professor, Department of Medicine, DMC&H, Ludhiana
Co-supervisor	Dr. Dinesh Gupta Professor & Head, Department of Medicine, DMC&H, Ludhiana Dr. Parminder Singh, Professor & Head, Department of Endocrinology, DMC&H, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Diabetes mellitus (DM) is a chronic endocrine condition characterized by chronic microvascular and macrovascular complications of hyperglycemia such as neuropathy, nephropathy, retinopathy, peripheral vascular disease, ischemic heart diease, stroke, etc. Cardiac autonomic neuropathy is one of the least recognized, understood, dreaded and troublesome complications of diabetes, which can cast a serious negative impact on the quality of life of diabetes patients.

Aim of Study: To estimate the pattern and frequency of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus patients.

Materials & methods: The Study will be conducted in the Department of Medicine, Department of Endocrinology and the Allied Specialities of Medicine, Dayanand Medical College and Hospital, Ludhiana. 100 Type 2 Diabetes Mellitus OPD and Indoor patients will be enrolled for this study and will be conducted over a period of one and a half years.

Clinical Significance: The present study will be conducted with an objective to estimate the pattern and frequency of Cardiacvascular Autonomic Neuropathy among the known Type 2 Diabetes Mellitus patients.

Keywords: Cross Sectional Study, Cardiovascular Autonomic Neuropathy, Type 2 Diabetes Mellitus.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"** exist in the Department of Medicine, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

Dr. Harmeet Pal Singh Dhooria
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Department of Medicine
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Co-Supervisor(s)

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Dr. Parminder Singh
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Head of the Department

Dr. Dinesh Gupta
Professor & Head
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Place: _____

Date: _____

APPROVAL PROFORMA
BYRESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Ujjwal Mahajan
Department	Medicine
Topic of Thesis	Study of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus
Likely date of appearing in PG examination	2022
Date of enrollment	May 2, 2019
Name of Head of Department	Dr. Dinesh Gupta
1) Supervisor **2) Co-Supervisor(s)**	Dr. Harmeet Pal Singh Dhooria Dr. Dinesh Gupta Dr. Parminder Singh

Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Assistant Dean Academics)	Dr. Deepinder K Chhina (Professor & Head, Microbiology)
Dr. Rajoo Singh Chhina (Dean Academics)	Dr. Neena Sood (Professor & Head, Pathology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
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Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Ujjwal Mahajan Post-graduate Student, Department of Medicine, Dayanand Medical College and Hospital, Ludhiana
2	NAME OF THE INSTITUTE	Dayanand Medical College and Hospital, Ludhiana, Punjab
3	COURSE OF STUDY AND SUBJECT	M.D. MEDICINE
4	DATE OF ADMISSION OF COURSE	2nd MAY, 2019
5	TITLE OF THE TOPIC	STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia precipitating because of the complete (Type 1 DM) or partial (Type 2 DM) absence of the insulin hormone. The recent estimates suggest that worldwide almost 350 million people suffer from diabetes, and these estimates are expected to get doubled by the year 2030 if no active measures are taken.[1]

Type 2 diabetes mellitus is the most common type of diabetes in the world constituting 90% of the diabetic population. Diabetes mellitus is a leading public health care problem in developing and developed world, with increasing incidence and long term complications. The triad of neuropathy, retinopathy and nephropathy are the characteristic complications of chronic diabetes mellitus.[2]

Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus (DM) that is strongly associated with approximately five-fold increased risk of cardiovascular mortality. CAN manifests in a spectrum of things, ranging from resting tachycardia and fixed heart rate (HR) to development of "silent" myocardial infarction.[3]

India is the diabetes capital of the world with 41 million Indians suffering from diabetes. Cardiac autonomic neuropathy (CAN) is often an underdiagnosed complication of diabetes mellitus (DM) and is associated with increased mortality and morbidity. The prevalence of CAN is approximately 31–73% in type 2 DM and the annual incidence has been reported to be 2%.[4]

The pathogenesis of CAN is complex and involves a cascade of pathways activated by hyperglycaemia resulting in neuronal ischaemia and cellular death. In addition, autoimmune and genetic factors are involved in the development of CAN. Autonomic nervous system dysfunction occurs as a classic complication of diabetes once other causes have been excluded. Diabetic autonomic neuropathy is a widespread disorder potentially involving adrenergic, cholinergic, dopaminergic autonomic fibers as well as peptidergic neurons.[5,6]

Diabetes-related CAN results from complex interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death. Hyperglycemia is thought to be a primary culprit, spurring a cascade of multiple complex mechanisms and pathways that induce oxidative stress and toxic glycosylation products—ultimately resulting in neuronal dysfunction and death.[7]

CAN is associated with reduction in HRV, resting tachycardia, OH and sudden death syndrome; Gastrointestinal, that includes diabetic gastropathy, enteropathy and colonic hypomotility; Urogenital, that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction; Sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis; Abnormal pupillary function; Hypoglycemia unawareness. The risk of developing autonomic dysfunction in DM depends on several factors. However, two of them are common to both type 1 DM and type 2 DM : Degree of glycemic control and disease duration. Inadequate glucose control plays an important role in the initial pathophysiology microcirculation dysfunction due to nitric oxide (NO) loss, oxidative stress (OS) and accumulation of free radicals with lesion of Schwann cell] as well as in its progression (neuronal apoptosis and axonal degeneration.[8]

6.2 REVIEW OF LITERATURE

CLASSIFICATION OF DIABETIC AUTONOMIC NEUROPATHIES

CAN, that is associated with reduction in HRV, resting tachycardia, OH and sudden death syndrome; Gastrointestinal, that includes diabetic gastropathy, enteropathy and colonic hypomotility; Urogenital, that includes erectile dysfunction, diabetic cystopathy and female sexual dysfunction; Sudomotor dysfunction with development of gustatory sweating and distal hyperhidrosis; Abnormal pupillary function; Hypoglycemia unawareness.

CLASSIFICATION

Subclinical phase: Decreased HRs variability.

Early phase: Resting tachycardia.

Advanced stage: Excercise intolerance; Cardiomyopathy with left ventricular dysfunction; Silent myocardial infarction [8]

- Sukla P et al concluded that overall prevalence of cardiac autonomic neuropathy among diabetic patients was found to be as 53.2%. Even though cardiac autonomic neuropathy can be detected by various invasive tests, noninvasive tests remain a key tool to detect it in the remote settings in a cost-effective and user-friendly manner without making people visit higher centers.[1]
- Sumaswi A et al concluded that cardiovascular autonomic neuropathy is common in type 2 diabetic patients and can be recognized by simple bedside autonomic function tests. Prolonged QTc interval is an indicator for the presence of cardiovascular autonomic neuropathy in type 2 diabetic patients.[2]
- Serhiyenko VA et al concluded CAN is common and often underdiagnosed complication of DM which is strongly associated with increased rate of cardiovascular morbidity and mortality. As the development and progression of cardiovascular denervation can be slowed down and is partly reversible in the early disease stages, it is recommended to perform screening for that complication among DM patients. A variety of methods can be used for CAN

assessment, but the "gold" standard clinical tests are CARTs. The basic CAN prevention and treatment tools are intensive glycemic control, lifestyle modification and management of CVD risk, but the unified algorithm and known disease modifying treatment is lacking.[3]

- Bhuyan K et al concluded that CAN is a common microvascular complication in type 2 DM. The duration of diabetes, age, and severity of nephropathy are its significant determinants and hence optimal glycemic management at early stages of diabetes may prevent development of CAN.[4]
- Dimitropoulos G et al concluded that CAN is very common and is an underdiagnosed complication of DM. CAN is associated with significant increase in morbidity and mortality and plays an important role in the development of diabetic cardiomyopathy and silent ischaemia. Clinicians interpreting exercise tolerance testing should be aware of the reduced accuracy of this test in patients with CAN. In addition, CAN might play a role in the pathogenesis of diabetes-related microvascular complications and the development of lower limb complications. However, before CAN is symptomatic and evident clinically, patients might have sub-clinical CAN for several years. The time scale for the progression from sub-clinical to clinically evident CAN is unknown. In addition, the time scale for the progression from early abnormalities (such as increased to clinically detectable cardiac disease is also unknown. Recent guidelines have recommended screening for CAN in patients with diabetes and issued guidance regarding the criteria used to diagnose CAN. CAN is assessed using several methods including CARTs, HRV, and imaging amongst others. The use of HRV and spectral analysis has simplified CAN testing which nonetheless remains time consuming. Despite our improved understanding of the pathogenesis of CAN, disease modifying treatment is lacking. Improving glycaemic control, life style changes and CVD risk factors management are the mainstay of treatment, which generally slow

the progression of CAN rather than reversing it. Further research exploring the natural history of CAN and the natural history of the impact of CAN on CVD is needed. Better understanding of CAN pathogenesis is also required in order to develop disease modifying treatments. OSA is increasingly recognised as an important contributor to the development of microvascular complications in DM, hence it is important to clarify the relationship between CAN and OSA as this might identify new treatment targets.[5]

- Giacomo Z et al concluded that CAN could be detected very early in type 2 diabetes. This study may suggest the importance of performing standardized cardiovascular autonomic tests after diagnosis of type 2 diabetes.[6]
- Agashe S et al concluded that Diabetes-related CAN causes significant morbidity and mortality and is common in both type 1 and type 2 DM. The pathophysiological mechanisms leading to CAN are multifactorial and need further study. CAN in DM can be subclinical or present with a wide range of symptoms, ranging from resting tachycardia to orthostatic hypotension. Although CAN in DM is difficult to diagnose in the hospital setting, multiple tests of autonomic function are available in the outpatient setting for screening and definitive diagnosis.[7]
- Maser RE et al concluded CAN was significantly associated with subsequent mortality in both groups, although the magnitude of the association was stronger for those studies for which two or more measures were used to define CAN. The pooled relative risk for studies that defined CAN with the presence of two or more abnormalities was 3.45 (95% CI 2.66-4.47; $P < 0.001$) compared with 1.20 (1.02-1.41; $P = 0.03$) for studies that used one measure.[8]
- Arif ZA et al concluded that cardiac autonomic neuropathy is common in diabetic patients in Pakistan. The clinician should identify early CAN by doing simple tests.,The study also demands for large scale population based studies in future.[9]

- Bellavere et al concluded that sudden death is more common in patients with diabetic autonomic neuropathy.[10]
- Fisher LA et al concluded that CAN is very common and often undiagnosed in patients with DM. Intensive multifactorial intervention targeting lifestyle, glycemic control, and CVD risk factors prevents the development and slows the progression of CAN. Identifying patients with CAN is important, as CAN is associated with increased mortality, CVD, CKD, perioperative morbidity, and lower-limb complications. As such, these patients should receive appropriate follow up and preventive treatments to prevent or slow the progression of these complications. CAN should be diagnosed as per the Toronto Consensus Panel statement using standardized CARTs. Further research into the pathogenesis of CAN is important, in order to identify novel treatment targets and develop new therapies.[11]
- Chen HS et al concluded that Type 2 diabetic patients with abnormal CVR tests may have increased mortality, and those combined with postural hypotension have higher mortality than those without. Abnormal CVR tests may be important predictors of mortality in Type 2 diabetes mellitus.[12]
- Brederl SS et al concluded that CAN is a frequent and important diagnosis achieved through the screening test recommended by the ADA. Due to its prognostic importance in DM2, the risk of sudden death and myocardial infarction and the possibility of treatment must not be neglected.[13]
- Xubin Yang et al concluded that In conclusion, higher serum CysC was associated with impaired cardiovascular autonomic function, especially the injury to parasympathetic nerve function in type 2 diabetic patients. CysC might be a reliable and convenient biomarker for detecting cardiovascular autonomic dysfunction.[14]
- Mathur CP et al concluded that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other ANF tests. Further, QTc prolongation has

linear positive correlation with the degree of CAN. It is inferred from the present observations that QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance.[15]

- Rodica P B concluded that CAN is a serious chronic complication of diabetes and an independent predictor of cardiovascular disease mortality. As illustrated by the case vignette and by the evidence presented in this review, CAN is associated with a poor prognosis and poor quality of life.[16]
- Aaron I et al concluded that Diabetic CAN, a serious complication found in one fourth of type 1 and one third of type 2 diabetic patients, is associated with increased mortality and silent myocardial ischemia and may even predict the development of stroke. CAN is associated with a poor prognosis and may result in severe orthostasis, postural hypotension, exercise intolerance, enhanced intraoperative instability, and an increased incidence of silent MI and ischemia. It may be attributable to a functional abnormality or to organic structural damage to the different components of the autonomic nervous system.[17]
- Bijaya K B concluded that cardiac autonomic neuropathy is a common and early complication of DM and it is associated with increased mortality due to cardiovascular related causes. Paucity of related symptoms leads to delayed detection of CAN. Proper history taking to identify symptoms related to CAN and performing simple autonomic tests in all patients of DM can identify cardiac autonomic neuropathy. Our study shows that 57.5% of the cases of diabetes mellitus had cardiac autonomic neuropathy and its incidence increased with severity of hyperglycemia, age and associated nephropathy.[18]
- Charles M et al concluded that signs of CAN were highly prevalent in a well-treated population with screen-detected type 2 diabetes.

The prevalence of CAN was not reduced by education and support of general practitioners and practice nurses in evidence-based target-driven management and treatment targets/algorithms compared with routine care according to national guidelines, but at follow-up the participants in the two treatment groups were equally well treated.[19]

- Spallone V et al concluded that Intensive diabetes therapy retards the development of CAN in type 1 diabetes, Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes and Lifestyle intervention may improve HRV in pre-diabetes and diabetes,Symptomatic orthostatic hypotension may be improved by non-pharmacological measures and by midodrine and/or fludrocortisone. Drug treatment of symptomatic orthostatic hypotension in diabetic patients with CAN may be challenging and should be thoroughly balanced between the goal of increasing standing blood pressure and the avoidance of a marked increase in supine blood pressure.[20]
- Karupasamy G et al concluded that the exact prevalence of autonomic neuropathy in diabetes is precisely not known, however tests of autonomic function have shown impairment in roughly 40 to 50% of diabetic patients. Subclinical autonomic nerve damage occurs more widely in diabetes and may go unnoticed. It is assuming greater importance because of the implications for morbidity and mortality. Symptomatic autonomic neuropathy carries a worse prognosis than any other complication of diabetes. Prevention of autonomic damage with newer drugs, particularly in its earlier stage will reduce the mortality and morbidity significantly. Newer drugs have to be tried for comforting many diabetics with clinical autonomic neuropathy afflicted with this condition in that at least the quality of life of with diabetic neuropathy will improve.[21]
- Basu A K et al concluded that the prevalenoe of cardiac autonomic neuropathy is 54%. Cardiac autonomic neuropathy is detected by various cardiac autonomic function tests. Symptoms of autonomic

neuropathy are not as sensitive as the autonomic function tests to detect cardiac neuropathy. Therefore, assessment of autonomic cardiovascular reflexes affords a satisfactory method for the evaluation of CAN.[22]

- Sanjay A M et al concluded that in the present study, the overall prevalence of autonomic neuropathy in diabetes mellitus was 58% at the tertiary care hospital.[23]
- Aggarwal S et al concluded that the prevalence of DAN in the cohort studied was 70%. Amongst these, 22.9% had severe autonomic dysfunction with prevalence of definite and early neuropathy being 40% and 37% respectively.[24]
- Benichou T et al reported strong evidence for an overall decrease in HRV in T2DM patients. Both sympathetic and parasympathetic activity were decreased, which can be explained by the deleterious effects of altered glucose metabolism on HRV. The benefits of an HRV evaluation in assessing and monitoring the severity of T2DM should be further studied, given its potential as a non– invasive, reliable and pain–free measurement[25]

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To estimate the pattern and frequency of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus patients.

7. MATERIALS AND METHODS

The study will be conducted in the Department of Medicine, Department of Endocrinology and the Allied Specialities of Medicine, Dayanand Medical College and Hospital, Ludhiana. 100 Type 2 Diabetes Mellitus OPD and indoor patients will be enrolled for this study and will be conducted over a period of one and a half years.

7.1 Source of Data

The study will be conducted in Department of Medicine, Department of Endocrinology and the Allied specialities of Dayanand Medical College and Hospital, Ludhiana.

7.2 METHOD OF COLLECTION OF DATA

Type 2 Diabetes mellitus patients presenting to OPD and IPD who fulfil the inclusion/exclusion criteria.

INCLUSION CRITERIA

1. Type 2 Diabetes Mellitus patients of age more than 18 years of Both sexes
2. Duration of diabetes for atleast 1 year
3. Patients willing to give informed written consent

EXCLUSION CRITERIA

1. Patients who are on beta blockers
2. Patients who are on drugs that prolong QTc
3. Chronic renal failure
4. History of ischaemic heart disease
5. Anemia (moderate 8-10 g/dl to severe<8 g/dl)
6. Asthma or COPD
7. Those who are not willing to give consent

The relevant history will be taken and clinical examination will be done in all subjects.

The basic investigations such as Hemoglobin, HBA1C, serum creatinine electrolytes, SGPT, lipid profile, urine routine, etc done will be recorded

Tests for assessment of cardiovascular autonomic function will be done.

Tests for Parasympathetic function

1. Heart rate response to deep breathing
2. Heart rate response to Valsalva Maneuver (Valsalva ratio)
3. Heart rate response to immediate standing (30: 15 ratio)

Tests for sympathetic function

1. Blood pressure response to standing
2. Blood pressure response to sustained hand grip

Interpretation of test results

Test results will be interpreted as per Ewing's criteria

Normal = All tests normal or 1 test borderline.

Early = One of the three heart rate tests abnormal or two borderline.

Definite = Two heart rate tests abnormal.

Severe = Two heart rate tests abnormal + one or both BP tests abnormal or both borderline.

Atypical= Any other combination of abnormalities

Tests for assessment of cardiovascular autonomic function will be done as under:

TEST	TECHINIQUE	NORMAL RESPONSE AND VALUE
BEAT TO BEAT HRV	With patient at rest and supine, heart rate is monitored by ECG when patient breathes in and out at 6 breaths/min	A difference in HR of >15 beats/min is normal and <10 beats/min is abnormal .The lowest normal value for expiration to inspiration ratio of R-R interval decreases with age (20-24 yr-1.17,25-29 yr-1.15,30-34-1.13,35-39 yr-1.12,40-44 yr-1.10 ,45-49-1.08,50-54 yr -1.07,55-59 yr-1.06,60-64 yr-1.04,65-69 yr-1.03,70-75 yr-1.02)
HEART RATE RESPONSE TO STANDING	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03, borderline 1.01-1.03
HEART RATE RESPONSE TO THE VALSALVA MANEUVER	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 secs during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is > 1.2, borderline 1.11-1.2
SYSTOLIC BLOOD PRESSURE RESPONSE TO STANDING	Systolic BP is measured in the supine subject. The patient stands and the systolic BP is measured after 2 min	Normal response is a fall of < 10 mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of > 30 mmHg
DIASTOLIC BLOOD PRESSURE RESPONSE TO ISOMETRIC EXERCISE	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic BP is a rise of > 16 mmHg in the other arm, borderline 11-15 mmHg

Interpretation of the tests:

	NORMAL	BORDERLINE	ABNORMAL
Tests reflecting mainly parasympathetic function			
Heart rate response to Valsalva Manoeuvre (Valsalva ratio)	≥ 1.21	1.11–1.20	≤ 1.10
Heart rate (R-R interval) variation	≥ 15 beats/min	11–14 beats/min	≤10 beats/min
Immediate heart rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Tests reflecting mainly sympathetic function			
Blood pressure response to standing (fall in systolic blood mm Hg of pressure)	≤ 10 mmHg	11–29 mmHg	≥ 30 mmHg
Blood pressure response to sustained handgrip (increase in diastolic blood pressure)	≥ 16 mmHg	11–15 mmHg	≤ 10 mmHg

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes, this study requires ECG test to be done on subjects entitled for this study.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith.

8.0 LIST OF REFERENCES

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PROFORMA

Serial No

Name Age Sex

MRD No

Duration of Diabetes

Diagnosis

Treatment History

History of present illnessYes/No

1. Polyphagia/Polydipsia/Polyuria
2. Tingling/Burning Sensation/Numbness/Sharp Jabbing Pain/Loss of Feeling
3. Facial Puffiness,Pedal Edema
4. Visual Complaints
5. Chest Pain on Exertion
6. Dyspnea on Exertion
7. Erectile Dysfunction
8. Any Other Complaints

PastHistory –Hypertension,Tuberculosisor Any Other Co-Morbidities

Signature of Candidate **Signature of Supervisor**

GPE

Pulse Rate- Blood Pressure-

Respiratory Rate- Temperature-

Pallor-Edema-

Icterus-Cyanosis-

Jaundice- Lymphadenopathy-

JVP- Clubbing-

Systemic Examination

CNS-

CVS-

Per Abdomen-

Respiratory System-

Investigations

1. Hemoglobin
2. Serum Creatinine
3. Serum Electrolytes
4. SGPT
5. Lipid Profile

LDL HDL

Triglycerides Cholesterol

6. Urine Routine

   Urine Albumin-

   Urine Glucose-

   Urine Microscopy-

7. Fundus Examination

8. ECG

9. Echo 2D (If Done)

10. Any other investigations

Signature of Candidate **Signature of Supervisor**

CARDIAC AUTONOMIC NEUROPATHY TESTING

PARASYMPHATHETIC TESTING

TEST NAME	NORMAL	BORDERLINE	ABNORMAL	RECORDED VALUE	INTERPRETATION
1.HEART RATE RESPONSE TO VALSALVA	>=1.21	1.11-1.20	<=1.1		
2.HEART RATE RESPONSE TO DEEP BREATHING	>=15 BEATS/MIN	11-14 BEATS /MIN	<=10 BEATS/ MIN		
3.HEART RATE RESPONSE TO STANDING	>=1.04	1.01-1.03	<=1.00		

SYMPHATHETIC TESTING

TEST NAME	NORMAL	BORDERLINE	ABNORMAL	RECORDED VALUE	INTERPRETATION
4. BP RESONSE TO STANDING(FALL IN SYSTOLIC BP)	<=10 MM HG	11-29 MM HG	>=30 MM HG		
5. BP RESPONSE TO SUSTAINED HAND GRIP	>=16 MM HG	11-15 MM HG	<=10 MM HG		

Signature of Candidate **Signature of Supervisor**

INTERPRETATION OF THE RESULTS (According to Ewing's criteria)

Normal = All tests normal or 1 test borderline.

Early = One of the three heart rate tests abnormal or twoborderline.

Definite = Two heart rate tests abnormal.

Severe = Two heart rate tests abnormal + one or both BP testsabnormal or both borderline.

Atypical= Any other combination of abnormalities.

CATEGORY	**INTERPRETATION**
NORMAL	
EARLY	
DEFINITE	
SEVERE	
ATYPICAL	

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

R/o.....

..... am willing to participate in the study. I am ready to participate in this study on my own **"STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"**. I affirm that I have not been given any financial incentive and no pressure has been put on me to give this consent. The purpose of this research has been explained to me and I believe that it is for the benefit of science and mankind. I have been explained about the risks in this research and I understand that the risk is very minimal. I have been explained the method of participating in this research work.

I can choose to opt out of this research at any time and my opting out will not have any effect on my treatment.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ_____

"STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ